

This report contains the collective views of an international group of experts and does not necessarily represent the decisions or the stated policy of the United Nations Environment Programme, the International Labour Organisation, or the World Health Organization.

Concise International Chemical Assessment Document 2

3,3'-DICHLOROBENZIDINE

First draft prepared by Ms R. Gomes and Ms M.E. Meek,
Environmental Health Directorate,
Health Canada

**Please note that the layout and pagination of this pdf file are not identical to the printed
CICAD**

Published under the joint sponsorship of the United Nations Environment Programme, the International Labour Organisation, and the World Health Organization, and produced within the framework of the Inter-Organization Programme for the Sound Management of Chemicals.



World Health Organization
Geneva, 1998

The **International Programme on Chemical Safety (IPCS)**, established in 1980, is a joint venture of the United Nations Environment Programme (UNEP), the International Labour Organisation (ILO), and the World Health Organization (WHO). The overall objectives of the IPCS are to establish the scientific basis for assessment of the risk to human health and the environment from exposure to chemicals, through international peer review processes, as a prerequisite for the promotion of chemical safety, and to provide technical assistance in strengthening national capacities for the sound management of chemicals.

The **Inter-Organization Programme for the Sound Management of Chemicals (IOMC)** was established in 1995 by UNEP, ILO, the Food and Agriculture Organization of the United Nations, WHO, the United Nations Industrial Development Organization, and the Organisation for Economic Co-operation and Development (Participating Organizations), following recommendations made by the 1992 UN Conference on Environment and Development to strengthen cooperation and increase coordination in the field of chemical safety. The purpose of the IOMC is to promote coordination of the policies and activities pursued by the Participating Organizations, jointly or separately, to achieve the sound management of chemicals in relation to human health and the environment.

WHO Library Cataloguing in Publication Data

3,3'-Dichlorobenzidine.

(Concise international chemical assessment document ; 2)

1.3,3'-Dichlorobenzidine – toxicity 2.Environmental exposure
3.Occupational exposure I.International Programme on
Chemical Safety II.Series

ISBN 92 4 153002 2 (NLM Classification: QV 633)
ISSN 1020-6167

The World Health Organization welcomes requests for permission to reproduce or translate its publications, in part or in full. Applications and enquiries should be addressed to the Office of Publications, World Health Organization, Geneva, Switzerland, which will be glad to provide the latest information on any changes made to the text, plans for new editions, and reprints and translations already available.

©World Health Organization 1998

Publications of the World Health Organization enjoy copyright protection in accordance with the provisions of Protocol 2 of the Universal Copyright Convention. All rights reserved.

The designations employed and the presentation of the material in this publication do not imply the expression of any opinion whatsoever on the part of the Secretariat of the World Health Organization concerning the legal status of any country, territory, city, or area or of its authorities, or concerning the delimitation of its frontiers or boundaries.

The mention of specific companies or of certain manufacturers' products does not imply that they are endorsed or recommended by the World Health Organization in preference to others of a similar nature that are not mentioned. Errors and omissions excepted, the names of proprietary products are distinguished by initial capital letters.

The Federal Ministry for the Environment, Nature Conservation and Nuclear Safety, Germany, provided financial support for the printing of this publication.

Printed by Wissenschaftliche Verlagsgesellschaft mbH, D-70009 Stuttgart 10

TABLE OF CONTENTS

	FOREWORD	1
1.	EXECUTIVE SUMMARY	4
2.	IDENTITY AND PHYSICAL/CHEMICAL PROPERTIES	4
3.	ANALYTICAL METHODS	5
4.	SOURCES OF HUMAN AND ENVIRONMENTAL EXPOSURE	5
5.	ENVIRONMENTAL TRANSPORT, DISTRIBUTION, AND TRANSFORMATION	5
6.	ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE	6
	6.1 Environmental levels	6
	6.2 Human exposure	6
7.	COMPARATIVE KINETICS AND METABOLISM IN LABORATORY ANIMALS AND HUMANS	7
8.	EFFECTS ON LABORATORY MAMMALS AND <i>IN VITRO</i> TEST SYSTEMS	7
	8.1 Single exposure	7
	8.2 Irritation and sensitization	8
	8.3 Short-term exposure	8
	8.4 Long-term exposure	8
	8.4.1 Subchronic exposure	8
	8.4.2 Chronic exposure and carcinogenicity	8
	8.5 Genotoxicity and related end-points	8
	8.6 Reproductive and developmental toxicity	8
	8.7 Immunological and neurological effects	8
9.	EFFECTS ON HUMANS	10
10.	EFFECTS ON OTHER ORGANISMS IN THE LABORATORY AND FIELD	10
	10.1 Aquatic environment	10
	10.2 Terrestrial environment	11
11.	EFFECTS EVALUATION	11
	11.1 Evaluation of health effects	11
	11.1.1 Hazard identification and dose–response assessment	11
	11.1.2 Criteria for setting guidance values for 3,3'-dichlorobenzidine	11
	11.1.3 Sample risk characterization	12
	11.2 Evaluation of environmental effects	12
12.	PREVIOUS EVALUATIONS BY INTERNATIONAL BODIES	12

13.	HUMAN HEALTH PROTECTION AND EMERGENCY ACTION	12
13.1	Human health hazards	12
13.2	Advice to physicians	12
13.3	Health surveillance advice	12
13.4	Fire hazards	13
13.5	Spillage and disposal	13
13.5.1	Spillage	13
13.5.2	Disposal	13
14.	CURRENT REGULATIONS, GUIDELINES, AND STANDARDS	13
	INTERNATIONAL CHEMICAL SAFETY CARD	14
	REFERENCES	16
	APPENDIX 1 — SOURCE DOCUMENTS	18
	APPENDIX 2 — CICAD PEER REVIEW	18
	APPENDIX 3 — CICAD FINAL REVIEW BOARD	19
	RÉSUMÉ D'ORIENTATION	20
	RESUMEN DE ORIENTACIÓN	21

FOREWORD

Concise International Chemical Assessment Documents (CICADs) are the latest in a family of publications from the International Programme on Chemical Safety (IPCS) — a cooperative programme of the World Health Organization (WHO), the International Labour Organisation (ILO), and the United Nations Environment Programme (UNEP). CICADs join the Environmental Health Criteria documents (EHCs) as authoritative documents on the risk assessment of chemicals.

CICADs are concise documents that provide summaries of the relevant scientific information concerning the potential effects of chemicals upon human health and/or the environment. They are based on selected national or regional evaluation documents or on existing EHCs. Before acceptance for publication as CICADs by IPCS, these documents have undergone extensive peer review by internationally selected experts to ensure their completeness, accuracy in the way in which the original data are represented, and the validity of the conclusions drawn.

The primary objective of CICADs is characterization of hazard and dose–response from exposure to a chemical. CICADs are not a summary of all available data on a particular chemical; rather, they include only that information considered critical for characterization of the risk posed by the chemical. The critical studies are, however, presented in sufficient detail to support the conclusions drawn. For additional information, the reader should consult the identified source documents upon which the CICAD has been based.

Risks to human health and the environment will vary considerably depending upon the type and extent of exposure. Responsible authorities are strongly encouraged to characterize risk on the basis of locally measured or predicted exposure scenarios. To assist the reader, examples of exposure estimation and risk characterization are provided in CICADs, whenever possible. These examples cannot be considered as representing all possible exposure situations, but are provided as guidance only. The reader is referred to EHC 170¹ for advice on the derivation of health-based guidance values.

¹ International Programme on Chemical Safety (1994) *Assessing human health risks of chemicals: derivation of guidance values for health-based exposure limits*. Geneva, World Health Organization (Environmental Health Criteria 170).

While every effort is made to ensure that CICADs represent the current status of knowledge, new information is being developed constantly. Unless otherwise stated, CICADs are based on a search of the scientific literature to the date shown in the executive summary. In the event that a reader becomes aware of new information that would change the conclusions drawn in a CICAD, the reader is requested to contact the IPCS to inform it of the new information.

Procedures

The flow chart shows the procedures followed to produce a CICAD. These procedures are designed to take advantage of the expertise that exists around the world — expertise that is required to produce the high-quality evaluations of toxicological, exposure, and other data that are necessary for assessing risks to human health and/or the environment.

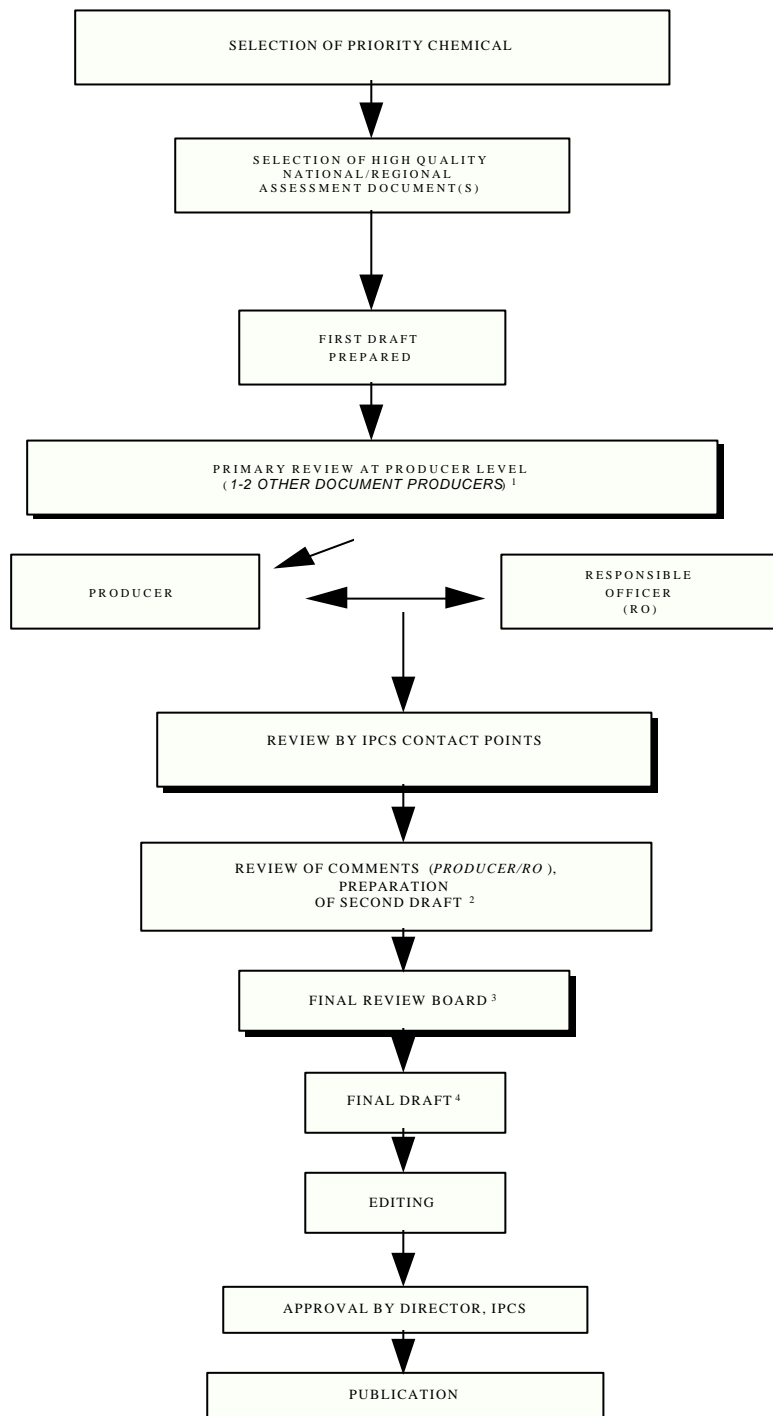
The first draft is based on an existing national, regional, or international review. Authors of the first draft are usually, but not necessarily, from the institution that developed the original review. A standard outline has been developed to encourage consistency in form. The first draft undergoes primary review by IPCS and one or more experienced authors of criteria documents to ensure that it meets the specified criteria for CICADs.

The second stage involves international peer review by scientists known for their particular expertise and by scientists selected from an international roster compiled by IPCS through recommendations from IPCS national Contact Points and from IPCS Participating Institutions. Adequate time is allowed for the selected experts to undertake a thorough review. Authors are required to take reviewers' comments into account and revise their draft, if necessary. The resulting second draft is submitted to a Final Review Board together with the reviewers' comments.

The CICAD Final Review Board has several important functions:

- to ensure that each CICAD has been subjected to an appropriate and thorough peer review;
- to verify that the peer reviewers' comments have been addressed appropriately;
- to provide guidance to those responsible for the preparation of CICADs on how to resolve any remaining issues if, in the opinion of the Board, the author has not adequately addressed all comments of the reviewers; and
- to approve CICADs as international assessments.

CICAD PREPARATION FLOW CHART



1 Revision as necessary.

2 Taking into account the comments from reviewers.

3 The second draft of documents is submitted to the Final Review Board together with the reviewers' comments (6-10 CICADs are usually reviewed at the Final Review Board). In the case of pesticides the role of the Final Review Board is fulfilled by a joint meeting on pesticides.

4 Includes any revisions requested by the Final Review Board.

Board members serve in their personal capacity, not as representatives of any organization, government, or industry. They are selected because of their expertise in human and environmental toxicology or because of their experience in the regulation of chemicals. Boards are chosen according to the range of expertise required for a meeting and the need for balanced geographic representation.

Board members, authors, reviewers, consultants, and advisers who participate in the preparation of a CICAD are required to declare any real or potential conflict of interest in relation to the subjects under discussion at any stage of the process. Representatives of nongovernmental organizations may be invited to observe the proceedings of the Final Review Board. Observers may participate in Board discussions only at the invitation of the Chairperson, and they may not participate in the final decision-making process.

1. EXECUTIVE SUMMARY

This CICAD on 3,3'-dichlorobenzidine was prepared by the Environmental Health Directorate of Health Canada, based principally on reviews of the Government of Canada (1993) and the Agency for Toxic Substances and Disease Registry (ATSDR, 1989), to assess the potential effects on human health of indirect exposure to 3,3'-dichlorobenzidine in the general environment as well as the chemical's environmental effects. Data relevant to the assessment of the effects of 3,3'-dichlorobenzidine on the environment and human health identified as of April 1992 (environmental effects) and October 1992 (human health effects) were considered in the Government of Canada (1993) review; data were subsequently updated to September 1995 from the International Register of Potentially Toxic Chemicals and on-line databases. Information concerning the nature of peer review and the availability of the Government of Canada (1993) and ATSDR (1989) documents is presented in Appendix 1. Information on the peer review of this CICAD is presented in Appendix 2. This CICAD was approved for publication at a meeting of the Final Review Board, held in Brussels, Belgium, on 18–20 November 1996. Participants at the Final Review Board meeting are presented in Appendix 3. The International Chemical Safety Card (ICSC 0481) for 3,3'-dichlorobenzidine, produced by the International Programme on Chemical Safety (IPCS, 1993), has also been reproduced in this document.

3,3'-Dichlorobenzidine (CAS no. 91-94-1) is a synthetic chlorinated primary aromatic amine and is commercially available as the dihydrochloride salt, 3,3'-dichlorobenzidine dihydrochloride ($C_{12}H_{10}N_2Cl_2 \cdot 2HCl$). 3,3'-Dichlorobenzidine (and some of its derivatives) is used primarily as an intermediate in the manufacture of pigments for printing inks, textiles, paints, and plastics. It is also used in the analytical determination of gold and as a curing agent in the synthesis of polyurethane elastomers.

Occupational exposure to 3,3'-dichlorobenzidine may occur in the pigment manufacturing industry and in industrial applications where 3,3'-dichlorobenzidine-based pigments are heated for prolonged periods. Levels of 3,3'-dichlorobenzidine ranging from #0.6 to 25 : g/m^3 have been measured in the workroom air of production and pigment manufacturing plants in Germany and Japan.

Owing to its relatively low volatility, very short persistence, and low concentrations in the atmosphere, 3,3'-dichlorobenzidine is not expected to contribute to

the greenhouse effect, depletion of the ozone layer, or the formation of ground-level ozone. Based on available data, it is likely that 3,3'-dichlorobenzidine poses negligible risk to aquatic organisms.

Available data are inadequate to serve as a basis for the development of tolerable intakes of 3,3'-dichlorobenzidine based on non-neoplastic effects. Based upon sufficient evidence of carcinogenicity of 3,3'-dichlorobenzidine in multiple animal species in limited studies and substantial evidence of genotoxicity both *in vitro* and *in vivo*, 3,3'-dichlorobenzidine is considered to be a potential human carcinogen. In view of its potential carcinogenicity in humans and in the absence of adequate epidemiological data, a sample health-based guidance value for 3,3'-dichlorobenzidine has been derived based upon the carcinogenic potency (i.e. $TD_{0.05}$) of this chemical, which has been calculated from the best reported, although limited, chronic study in which ChR-CD rats were fed 1000 ppm 3,3'-dichlorobenzidine in the diet for up to 488 days. The $TD_{0.05}$ was calculated based on linear interpolation, incorporating a body weight to surface area correction (power of 2/3, owing to the lack of identification of the active metabolite[s]) and correcting for less than 2 years of exposure, and ranges from 0.74 to 1.4 mg/kg body weight per day. A value obtained by dividing the low end of this $TD_{0.05}$ range (i.e. 0.74 mg/kg body weight per day) by, for example, 5000–50 000 (i.e. 1.48×10^{-4} to 1.48×10^{-5} mg/kg body weight per day) might be considered appropriate as a guidance value in ingested media. This margin affords protection similar to that associated with the range for low-dose risk estimates generally considered by various agencies to be "essentially negligible" (i.e. 10^{-5} to 10^{-6}). Based upon a sample estimate of exposure that involved predicted concentrations or limited monitoring data from the USA and Canada, where the chemical has generally not been detected, the estimated total daily intake of 3,3'-dichlorobenzidine by the general population (from indirect exposure in the general environment) is several orders of magnitude less than the sample guidance value derived above.

2. IDENTITY AND PHYSICAL/CHEMICAL PROPERTIES

3,3'-Dichlorobenzidine (CAS no. 91-94-1; 3,3'-dichloro-4,4'-biphenyldiamine, 3,3'-dichloro-4,4'-diaminobiphenyl, 4,4'-diamino-3,3'-dichlorobiphenyl), a synthetic chlorinated primary aromatic amine, is a grey to purple crystalline solid at room temperature. It has a

relatively low vapour pressure (1 mPa at 22°C), a low water solubility (0.4 mg/100 ml at 22°C), and a log *n*-octanol/water partition coefficient of 3.02. 3,3'-Dichlorobenzidine is usually commercially available as the dihydrochloride salt, 3,3'-dichlorobenzidine dihydrochloride (C₁₂H₁₀N₂Cl₂•2HCl) (Government of Canada, 1993). Additional physical/chemical properties of 3,3'-dichlorobenzidine are presented in the International Chemical Safety Card reproduced in this document.

3. ANALYTICAL METHODS

Analysis of 3,3'-dichlorobenzidine in environmental samples is most commonly achieved by gas chromatography/mass spectrometry, capillary column gas chromatography/Fourier transform infrared spectrometry, and high-performance liquid chromatography. A detection limit of 3 : g/m³ has been reported for 3,3'-dichlorobenzidine in air, whereas detection limits for 3,3'-dichlorobenzidine in water range from 0.05 to 50 : g/litre (IARC, 1982; ATSDR, 1989). A detection limit of <20 ppb (: g/kg) has been reported for 3,3'-dichlorobenzidine in food (i.e. fish) using gas chromatographic techniques with either nitrogen–phosphorus detection or electron capture detection. No analytical methods for the determination of 3,3'-dichlorobenzidine in soil or sediment were identified (ATSDR, 1989). A detection limit of 60 ppt (ng/litre) has been reported for 3,3'-dichlorobenzidine in biological samples (i.e. urine) using gas chromatographic techniques with either electron capture detection or rubidium-sensitized thermionic detection (HSDB, 1995).

4. SOURCES OF HUMAN AND ENVIRONMENTAL EXPOSURE

There are no known natural sources of 3,3'-dichlorobenzidine. 3,3'-Dichlorobenzidine (and some of its derivatives) is used primarily as an intermediate in the manufacture of diarylide yellow or azo red pigments for printing inks, textiles, paints, and plastics. It is also used in the analytical determination of gold and as a curing agent in the synthesis of polyurethane elastomers (Gerarde & Gerarde, 1974; Government of Canada, 1993).

The world production of 3,3'-dichlorobenzidine was estimated to range from 7000 to 10 000 t in 1983, with 3900–4200 t being synthesized in Europe. In Japan,

approximately 3170 t and 3400 t of 3,3'-dichlorobenzidine were produced in 1992 and 1993, respectively. In Germany, approximately 2500 t of 3,3'-dichlorobenzidine were produced in 1989 (none of which was exported). In 1983, 1.1 million pounds (500 t) of 3,3'-dichlorobenzidine base and salts were imported into the USA. In 1987, 9.9 million pounds (4490 t) of 3,3'-dichlorobenzidine were consumed in the USA. 3,3'-Dichlorobenzidine is not produced in Canada but has been imported on a regular basis. The reported volumes of importation into Canada have ranged from 21 to 109 t over the period 1986–1989 (ATSDR, 1989; Chemicals Daily, 1993, 1994; Government of Canada, 1993; Law, 1995).

3,3'-Dichlorobenzidine can enter the environment from any stage in the production, storage, transport, use, or disposal of 3,3'-dichlorobenzidine-containing materials. Although there are no quantitative data, the largest releases would likely be through direct emissions from plants that manufacture 3,3'-dichlorobenzidine-containing materials and from the degradation of 3,3'-dichlorobenzidine-containing pigments (Government of Canada, 1993).

Total industrial emissions of 3,3'-dichlorobenzidine to the environment in the USA in 1988 were estimated to be 6 t. In Germany, emissions of 3,3'-dichlorobenzidine into wastewater from various industrial facilities were estimated to be less than 0.095 t in 1989. Total industrial emissions of 3,3'-dichlorobenzidine to the environment in Canada were estimated to be 0.1 t in 1989 (Government of Canada, 1993; Law, 1995).

5. ENVIRONMENTAL TRANSPORT, DISTRIBUTION, AND TRANSFORMATION

The half-life for volatilization of 3,3'-dichlorobenzidine from surface water to the atmosphere has been estimated to be 72 days. In water, 3,3'-dichlorobenzidine may be degraded by photooxidation, photolysis, and biodegradation; the estimated half-life of 3,3'-dichlorobenzidine in water is less than 10 minutes. The half-life of 3,3'-dichlorobenzidine in aqueous media is proportional to the light intensity, with some of the major photodegradation products including monochlorobenzidine, benzidine, as well as a number of brightly coloured water-insoluble materials; under intense light or sunlight, very little of the 3,3'-dichlorobenzidine, monochlorobenzidine, and benzidine remain in the water after 15 minutes (Banerjee et al., 1978; Government of Canada, 1993).

3,3'-Dichlorobenzidine is fairly resistant to degradation by naturally occurring aquatic microorganisms. Half-lives of 4–26 weeks and 16–101 weeks have been estimated for the biodegradation of 3,3'-dichlorobenzidine in surface water and anaerobic groundwater, respectively (Government of Canada, 1993).

3,3'-Dichlorobenzidine is strongly bound to soil, sediment, and sludge and therefore is highly immobile. In soil, 3,3'-dichlorobenzidine is mineralized very slowly under aerobic and anaerobic conditions. The half-life for the aerobic degradation of 3,3'-dichlorobenzidine in soil has been estimated to range from 4 to 26 weeks. 3,3'-Dichlorobenzidine may also be oxidized by metal ions (e.g. ferric iron) present in clay (BUA, 1993; Government of Canada, 1993; HSDB, 1995).

Half-lives of 1.5–5 minutes and 0.9–9 hours have been estimated for the photolysis and photooxidation of 3,3'-dichlorobenzidine in air, respectively (Government of Canada, 1993).

3,3'-Dichlorobenzidine can accumulate in aquatic biota. A bioconcentration factor of approximately 500 has been reported for bluegill sunfish (*Lepomis macrochirus*), based on a study in which the fish were exposed to 5 or 100 : g [¹⁴C]3,3'-dichlorobenzidine per litre; equilibria were achieved within 96–168 hours (Appleton & Sikka, 1980). In other studies, a 3-day bioaccumulation factor of 610 in fish (golden orfe, *Leuciscus idus melanotus*), a 5-day bioaccumulation factor of 3100 in activated sludge, and a 1-day bioaccumulation factor of 940 in algae (*Chlorella fusca*) have been reported (Freitag et al., 1985).

6. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

6.1 Environmental levels

Available data on the levels of 3,3'-dichlorobenzidine in air were limited to reports from the USA in which 3,3'-dichlorobenzidine was not detected (detection limits 0.1 and 5 ng/m³) in ambient air in the vicinity of two dyestuff production facilities (Narang et al., 1982; Riggan et al., 1983).

Levels of 3,3'-dichlorobenzidine in surface water have ranged from not detected (the only reported detection limit was 0.25 : g/litre) to 0.3 : g/litre, based on studies conducted between 1987 and 1992 in France, England, the Netherlands, Switzerland, Germany, Spain,

and the USA (Staples et al., 1985; Valls et al., 1990; Slobodnik et al., 1993).

In the only relevant study identified, 3,3'-dichlorobenzidine was not detected (detection limit 0.02 ng/litre) in samples of drinking-water collected from two municipalities in Ontario, Canada (Malaiyandi et al., 1987).

Data were not identified concerning the levels of 3,3'-dichlorobenzidine in uncontaminated soil; however, this compound was not detected (detection limits not reported) in sediment in the USA (location of sample acquisition not reported) and Spain (samples collected from the Besos River, Barcelona) (Staples et al., 1985; Valls et al., 1990). Information concerning the levels (or occurrence) of 3,3'-dichlorobenzidine in foodstuffs was not identified. Although 3,3'-dichlorobenzidine has the potential to bioaccumulate in aquatic organisms, this compound was not detected (detection limit not reported) in samples of biota collected in the USA (Staples et al., 1985).

Concentrations of 3,3'-dichlorobenzidine at contaminated (industrial and municipal) sites within the USA have ranged from not detected (detection limit 20 : g/litre) to 120 : g/litre in landfill leachate and groundwater and from not detected (detection limit 0.66 mg/kg) to 20 mg/kg dry weight in landfill soil and sewage sludge (Fricke et al., 1985; Smith & Weber, 1990; US EPA, 1990a,b; BUA, 1993).

Estimates of the fate and concentrations of 3,3'-dichlorobenzidine in the Canadian environment have been generated by the Level III fugacity computer model of Mackay and Paterson (1991), incorporating data on the chemical's physical and chemical properties and transformation half-lives (Howard et al., 1991) and assuming that 1% of the total amount produced and imported into Canada is released into various media in proportions similar to those reported in the US Toxic Release Inventory. The results indicate that, at steady state, the proportion of released 3,3'-dichlorobenzidine found in air, water, and soil would be <0.001%, 99.75%, and <0.001%, respectively. Average concentrations of 3,3'-dichlorobenzidine in air, water, and soil, predicted on the basis of the model, were 7.6×10^{-16} : g/m³, 3.4×10^{-7} ng/litre, and 1.1×10^{-16} : g/g dry weight, respectively (Government of Canada, 1993). As 3,3'-dichlorobenzidine binds strongly to soil and aquatic sediment, it is likely to have reduced bioavailability.

6.2 Human exposure

Exposure of the general population to 3,3'-dichlorobenzidine in environmental media may be estimated based on measured and predicted concentra-

tions in various media and reference values for body weight and consumption patterns. Owing to the availability of relevant data, exposure has been estimated here based primarily on data from Canada and the USA. In view of the extremely limited nature of the available data, these estimates are presented primarily in an attempt to identify typical relative proportions of exposure from various media. Countries are encouraged to estimate total exposure on the basis of national data, possibly in a manner similar to that outlined here.

Based on a daily inhalation volume for adults of 22 m³, a mean body weight for males and females of 64 kg (IPCS, 1994), and the most sensitive detection limit for 3,3'-dichlorobenzidine (0.1 ng/m³) in reports in which this compound was not detected in the air surrounding dye production facilities in the USA, mean intake from air for the general population is estimated to be less than 3.4×10^{-5} : g/kg body weight per day. Based on a predicted concentration (by fugacity modelling) of 3,3'-dichlorobenzidine in ambient air in Canada of 7.6×10^{-16} : g/m³, the mean intake of 3,3'-dichlorobenzidine from air for the general population is estimated to be much lower (i.e. 2.6×10^{-16} : g/kg body weight per day).

Based on a daily volume of water consumption for adults of 1.4 litres, a mean body weight of 64 kg (IPCS, 1994), and the limit of detection for 3,3'-dichlorobenzidine (0.02 ng/litre) in a survey in which this compound was not detected in drinking-water from two municipalities in Canada, the mean intake of 3,3'-dichlorobenzidine from drinking-water for the general population is estimated to be less than 4.4×10^{-7} : g/kg body weight per day. However, based on a predicted concentration of 3,3'-dichlorobenzidine in surface water in Canada of 3.4×10^{-7} ng/litre, the estimated mean intake of 3,3'-dichlorobenzidine from drinking-water for the general population would be 7.4×10^{-12} : g/kg body weight per day.

Available data were inadequate to estimate the intake of 3,3'-dichlorobenzidine from food. Studies were not identified concerning measured levels of 3,3'-dichlorobenzidine in soil; however, based on a predicted concentration of 3,3'-dichlorobenzidine in soil in Canada of 1.1×10^{-16} : g/g, a daily ingestion of 20 mg of soil by adults, and a mean body weight of 64 kg (IPCS, 1994), the estimated intake of 3,3'-dichlorobenzidine from soil would be 3.4×10^{-20} : g/kg body weight per day.

The general population may be exposed to 3,3'-dichlorobenzidine during the use of commercial products, including pressurized spray containers of paints, lacquers, and enamels containing traces of benzidine yellow, an azo dye derived from 3,3'-dichlorobenzidine (ATSDR, 1989). However, no quanti-

tative data were identified concerning the levels of 3,3'-dichlorobenzidine in products containing pigments or dyes derived from this substance.

Occupational exposure (principally by inhalation or dermal contact) to 3,3'-dichlorobenzidine may occur in the pigment manufacturing industry and in industrial applications where 3,3'-dichlorobenzidine-based pigments are heated for prolonged periods (e.g. the production of coloured plastics and films; the spin dyeing of polypropylene fibres) (US EPA, 1990c; US DHHS, 1994). Levels of 3,3'-dichlorobenzidine ranging from #0.6 to 25 : g/m³ have been measured in the workroom air of production and pigment manufacturing plants in Germany (ATSDR, 1989) and Japan (US EPA, 1980).

7. COMPARATIVE KINETICS AND METABOLISM IN LABORATORY ANIMALS AND HUMANS

It is generally believed that the hepatic metabolism of 3,3'-dichlorobenzidine in rodents (i.e. rats) involves its oxidation to highly reactive *N*-oxygenated intermediates by the microsomal cytochrome P-450 and flavin monooxygenase enzyme complexes. Although the 3,3'-dichlorobenzidine-derived *N*-oxygenated intermediates have not been unequivocally identified, they are believed to be responsible for the mutagenic and genotoxic effects (e.g. related to DNA binding) of 3,3'-dichlorobenzidine in bacterial and mammalian systems (Government of Canada, 1993).

Few quantitative data on the metabolism of 3,3'-dichlorobenzidine in humans were identified. Small amounts (approximately 1–2%) of free and glucuronide-conjugated *N*-hydroxyacetyl derivatives of 3,3'-dichlorobenzidine were excreted in the urine of volunteers orally administered 3,3'-dichlorobenzidine. Based upon studies in which 3,3'-dichlorobenzidine has been detected in the urine (at concentrations up to 296 : g/litre) of workers occupationally exposed to this substance, 3,3'-dichlorobenzidine appears to be readily absorbed from the skin following dermal exposure (BUA, 1993).

3,3'-Dichloro-*N*-acetylbenzidine, 3,3'-dichloro-*N,N*-diacetylbenzidine, and conjugated metabolites (the identities of which were not confirmed) have been detected in the urine of rats administered 3,3'-dichlorobenzidine orally. The covalent binding of 3,3'-dichlorobenzidine metabolites to haemoglobin, hepatic lipids, and DNA in the intestinal and bladder epithelium or liver has been observed in experimental animals (e.g. rodents) exposed *in vivo* (Government of Canada, 1993).

8. EFFECTS ON LABORATORY MAMMALS AND *IN VITRO* TEST SYSTEMS

8.1 Single exposure

The acute toxicity of 3,3'-dichlorobenzidine (either as the free base or as dihydrochloride salt) in experimental animals is low, with oral LD₅₀s in rats and mice being higher than 3820 mg/kg body weight and 488 mg/kg body weight, respectively (Government of Canada, 1993). Gastrointestinal congestion and haemorrhage were the principal effects in these studies (ACGIH, 1991). In their review of acute toxicity data, the American Conference of Governmental and Industrial Hygienists (ACGIH, 1991) reported mortality in four of five rabbits following dermal application of 3,3'-dichlorobenzidine at 1 g/kg body weight for 24 hours; however, additional data were not presented. Following the acute administration (route not specified) of up to 50 mg of 3,3'-dichlorobenzidine per kg body weight in cats, there was only a slight increase (up to 1.3%) in methaemoglobin content in the blood, whereas the number of Heinz bodies was increased fourfold (BUA, 1993).

8.2 Irritation and sensitization

Data on the sensitization potential of 3,3'-dichlorobenzidine in experimental animals were not identified, and only limited data were available concerning the irritation potential of this chemical. BUA (1993) reported no irritation or "symptoms of intolerance" in rabbits exposed by conjunctival application of 100 mg of 3,3'-dichlorobenzidine; however, additional data were not presented in this published account.

8.3 Short-term exposure

Studies on the toxicological effects produced following the short-term repeated exposure of experimental animals to 3,3'-dichlorobenzidine have not been identified.

8.4 Long-term exposure

8.4.1 Subchronic exposure

Subchronic studies in which non-neoplastic effects of 3,3'-dichlorobenzidine have been assessed have not been identified.

8.4.2 Chronic exposure and carcinogenicity

Chronic studies in which non-neoplastic effects of 3,3'-dichlorobenzidine have been adequately assessed

have not been identified. In several early limited carcinogenesis bioassays (summarized in Table 1), 3,3'-dichlorobenzidine increased the incidence of tumours in experimental animals, sometimes following relatively short periods of administration. The incidence of mammary gland carcinomas in ChR-CD rats administered diets containing 0 or 1000 ppm 3,3'-dichlorobenzidine for up to 488 days was 3/44 and 26/44 in females and 0/44 and 7/44 in males, respectively (Stula et al., 1975). In male rats, the incidence of Zymbal gland carcinomas was 0/44 and 8/44 and the incidence of granulocytic leukaemias was 2/44 and 9/44 in the control and 3,3'-dichlorobenzidine-exposed animals, respectively. In a limited study in which a small group of beagle dogs received approximately 10.4 mg 3,3'-dichlorobenzidine per kg body weight in gelatin capsules 3 or 5 times/week for up to 7.1 years, the incidence of hepatocellular carcinoma and bladder carcinoma was increased ($p < 0.025$) compared with controls (Stula et al., 1978). Hepatic tumours occurred early (after 6 and 12 months) in male ICR/JCL mice administered a diet containing 0 or 1000 ppm 3,3'-dichlorobenzidine over a 12-month period; after 12 months, the incidence of hepatomas was 2/21 and 18/18 ($p < 0.001$) in the control and exposed groups, respectively (Osanai, 1976).

Compared with controls, the incidence of lymphoid leukaemias in offspring born to female mice administered five subcutaneous injections of 3,3'-dichlorobenzidine during the last week of pregnancy was increased (0/30 versus 7/24; statistical significance unspecified) (Golub et al., 1975). Results in studies with hamsters have been equivocal (Saffiotti et al., 1967; Sellakumar et al., 1969). Other identified studies (Pliss, 1959, 1963; Tsuda et al., 1977) contribute little to the assessment of the weight of evidence of carcinogenicity for 3,3'-dichlorobenzidine, owing to their limitations of protocol and reporting (Table 1).

8.5 Genotoxicity and related end-points

There is convincing evidence that 3,3'-dichlorobenzidine is genotoxic both *in vivo* and *in vitro* (Table 2). In *in vitro* assays, 3,3'-dichlorobenzidine was mutagenic in *Salmonella typhimurium*, increased the frequency of sister chromatid exchange and unscheduled DNA synthesis in human cells, and "morphologically transformed" rat embryo cells. In *in vivo* studies, 3,3'-dichlorobenzidine increased the frequency of micronuclei in the bone marrow cells of mice, increased unscheduled DNA synthesis in the liver of rats, and increased the frequency of chromosomal aberrations in the bone marrow cells of mice.

Table 1: Carcinogenicity of 3,3'-dichlorobenzidine.

Test protocol	Results	Comments	Reference
Female beagle dogs ($n = 6$) were administered 3,3'-dichlorobenzidine (100 mg in gelatin capsules) 3 times/week for 6 weeks, and then 5 times/week for up to 7.1 years (mean dose approximately 10.4 mg/kg body weight per exposure); six unexposed controls were sacrificed after 8.3–9.0 years.	The incidence of bladder carcinomas and hepatocellular carcinomas in 3,3'-dichlorobenzidine-exposed animals that survived longer than 6.6 years was 5/5 ($p < 0.025$) and 4/5 ($p < 0.025$), respectively. No liver or bladder tumours were found in the unexposed controls, although 4/6 controls were reported to have developed mammary carcinomas (attributed to the age of these animals).	Small number of animals and single sex exposed for a limited proportion of life span	Stula et al., 1978
Groups of ChR-CD rats ($n = 50$ per sex) were administered diets containing 0 or 1000 ppm (0.1% w/w) 3,3'-dichlorobenzidine (0 or 50 mg/kg body weight per day) for up to 488 days.	The incidence of mammary carcinomas in rats administered 0 or 1000 ppm 3,3'-dichlorobenzidine in the diet was 3/44 and 26/44 ($p < 0.05$) in females and 0/44 and 7/44 ($p < 0.05$) in males. In male rats, the incidence of Zymbal gland carcinomas was 0/44 and 8/44 ($p < 0.05$) and the incidence of granulocytic leukaemias was 2/44 and 9/44 ($p < 0.05$) in the control and 3,3'-dichlorobenzidine-exposed animals, respectively.	Exposure for a limited proportion of life span of one sex	Stula et al., 1975
Male ($n = 35$) and female ($n = 15$) Rappolovo rats were administered a diet containing 3,3'-dichlorobenzidine (0.5–1.0 ml of a 4.4% solution) dissolved in sunflower oil for 6 days/week for 12 months. "Control" animals ($n = 130$) were administered (by injection) octadecylamine and stearylamine for 10 months and observed until 23 months.	Tumours (in the Zymbal and mammary glands, bladder, and haematopoietic system) were observed in 79% (23/29) of animals surviving at the time (not specified) the first tumours were detected following exposure to 3,3'-dichlorobenzidine; no tumours were observed in the controls.	Small group sizes, single dose level, lack of appropriate controls, and incomplete reporting of results (i.e. the sex of the animals with tumours, and the nature and incidence of tumours)	Pliss, 1959
Rappolovo rats (sex and number not reported) were administered a diet containing an amount (not clearly specified) of 3,3'-dichlorobenzidine for 10–13 months. A group of 50 rats (25 of which were injected with sunflower oil) served as controls.	Tumours (in bone, mammary glands, bladder, "etc.") were observed in 86% of rats exposed to 3,3'-dichlorobenzidine in the diet, whereas tumours (liver sarcoma) were observed in only one of the controls.	Lack of appropriate controls and incomplete reporting of the protocol and results (i.e. nature and incidence of the tumours)	Pliss, 1963
Groups of male Wistar rats ($n = 18$) were administered diets containing 0 or 0.03% (w/w) (0 or 300 ppm) 3,3'-dichlorobenzidine (0 or 15 mg/kg body weight per day) for 40 weeks.	No evidence of histopathological effects in either the bladder or liver was observed following the administration of diets containing 0 or 300 ppm 3,3'-dichlorobenzidine for 40 weeks.	Limited period of exposure, small number of animals, single sex, and limited histopathological examination	Tsuda et al., 1977
Groups of male ICR/JCL mice ($n = 26$) were administered a diet containing 0 or 0.1% (w/w) (0 or 1000 ppm) 3,3'-dichlorobenzidine (0 or 130 mg/kg body weight per day) for up to 12 months.	After 12 months, the incidence of hepatomas was 2/21 and 18/18 ($p < 0.001$) in the control and 3,3'-dichlorobenzidine-exposed groups, respectively.	Small numbers of animals, single sex, and incomplete description of the nature of hepatic tumours	Osanai, 1976

Table 1: Continued

Test protocol	Results	Comments	Reference
Male (<i>n</i> = 51) and female (<i>n</i> = 22) strain D mice were administered a diet containing 3,3'-dichlorobenzidine (0.1 ml of a 1.1% solution) for a period of 10 months and were maintained until 18.5 months. No information was presented concerning the use of controls.	After 18.5 months, the incidence of hepatomas and haemangiomas in mice exposed to 3,3'-dichlorobenzidine was 2/18 and 2/18, respectively.	Small group sizes, single dose level, lack of appropriate controls, and incomplete reporting of results (i.e. the sex of animals with tumours, and the nature and incidence of the tumours)	Pliss, 1959
Groups of Syrian golden hamsters (<i>n</i> = 30 per sex) were administered diets containing 0 or 0.1% (w/w) (0 or 1000 ppm) 3,3'-dichlorobenzidine (0 or 90 mg/kg body weight per day) for life.	Exposure to 1000 ppm 3,3'-dichlorobenzidine in the diet failed to produce "any significant carcinogenic effect or bladder pathology" in hamsters; however, no quantitative experimental results were presented.	Small group sizes and inadequate reporting of data in the published account (abstract only)	Saffiotti et al., 1967
Groups of male and female hamsters (<i>n</i> = 30 per sex) were administered diets containing 0 or 0.3% (w/w) (0 or 3000 ppm) 3,3'-dichlorobenzidine (0 or 270 mg/kg body weight per day).	Exposure to 3,3'-dichlorobenzidine "induced 4 transitional cell bladder carcinomas, some liver-cell and cholangiomatous tumours and diffuse chronic intrahepatic obstructing cholangitis (63%)."	Small number of animals and incomplete reporting of data (i.e. the sex of the animals with tumours, the incidence of the various tumour types, and the results for unexposed controls)	Sellakumar et al., 1969

Table 2: Genotoxicity of 3,3'-dichlorobenzidine.

Test species/cell line	End-point	Result		Reference
		With activation	Without activation	
IN VITRO STUDIES				
<i>Salmonella typhimurium</i>	Gene mutation			Garner et al., 1975; Anderson & Styles, 1978; Lazear et al., 1979; Reid et al., 1984;
TA98		+	+	
TA100		+	-	
TA1535		+/-	ND	Savard & Josephy, 1986; Iba, 1987; Messerly et al., 1987;
TA1538		+	+	Ghosal & Iba, 1992; You et al., 1993
Human B-lymphoblastoid cells	Sister chromatid exchange	+	+	Shiraishi, 1986
HeLa S3 cells	Unscheduled DNA synthesis	+	ND	Martin et al., 1978
Rat embryo cells	Transformation	ND	+	Freeman et al., 1973
IN VIVO STUDIES				
ICR-SPF mice (oral administration)	Micronuclei	+	NA	Cihak & Vontorkova, 1987
Alpk:AP rats (oral administration)	Unscheduled DNA synthesis	+	NA	Ashby & Mohammed, 1988
Mice ^a (intraperitoneal injection)	Chromosomal aberrations	+	NA	You et al., 1993

NA = not applicable; ND = no data were identified; ^a Strain not specified.

8.6 Reproductive and developmental toxicity

The incidence of "hyperplastic changes" in kidney explants obtained from mouse embryos exposed to 3,3'-dichlorobenzidine *in utero* (following subcutaneous injection of dams) was increased, compared with controls (Shabad et al., 1972).

8.7 Immunological and neurological effects

Studies concerning the immunological effects of 3,3'-dichlorobenzidine have not been identified. Data on

neurotoxic effects were limited to the observation (Stula et al., 1978) of convulsions and neuronal degeneration in one female beagle dog orally administered 3,3'-dichlorobenzidine (100 mg 3 times weekly for 6 weeks and then 5 times weekly for the duration of the experiment) for 42 months.

9. EFFECTS ON HUMANS

Case reports concerning the effects of exposure of humans to 3,3'-dichlorobenzidine were not identified. Although clinical studies concerning the potential for

3,3'-dichlorobenzidine to induce dermal and ocular irritation in humans have not been identified, dermatitis was reported among workers occupationally exposed to 3,3'-dichlorobenzidine in one (limited) study (Gerarde & Gerarde, 1974).

Identified epidemiological data are restricted to three limited studies of cancer in production workers. No increase in the incidence of or death due to bladder cancer was reported in historical cohort studies of groups of 109 (MacIntyre, 1975), 35 (Gadian, 1975), or 207 (Gerarde & Gerarde, 1974) workers occupationally exposed to 3,3'-dichlorobenzidine. Owing to the limitations of all three of these studies, including the small number of individuals examined, the relatively short periods of follow-up (i.e. less than 20 years), and methodological limitations, such as lack of appropriate control groups (Gerarde & Gerarde, 1974; Gadian, 1975), these studies have only limited power to detect an exposure-related effect. The workers in these studies were also exposed to other substances.

10. EFFECTS ON OTHER ORGANISMS IN THE LABORATORY AND FIELD

10.1 Aquatic environment

There are very few data on the acute toxicity of 3,3'-dichlorobenzidine to aquatic organisms. An IC_{50} of 0.06 mg/litre was reported for bacteria in the Microtox assay (Dutka & Kwan, 1981). Sikka et al. (1978) reported a 48-hour LC_{100} value for bluegill sunfish (*Lepomis macrochirus*) of 2 mg/litre; 50% mortality was observed following exposure to 3,3'-dichlorobenzidine at 0.5 mg/litre for 96–120 hours. Based on quantitative structure–activity relationships, 96-hour LC_{50} values for fathead minnow (*Pimephales promelas*), rainbow trout (*Oncorhynchus mykiss*), and golden orfe (*Leuciscus idus melanotus*) have been estimated to be >3 mg/litre, 3 mg/litre, and 1.5 mg/litre, respectively (Government of Canada, 1993).

10.2 Terrestrial environment

No data were identified concerning the toxicity of 3,3'-dichlorobenzidine to wild mammals, terrestrial organisms, birds, or sediment or soil biota.

11. EFFECTS EVALUATION

11.1 Evaluation of health effects

11.1.1 Hazard identification and dose–response assessment

Epidemiological investigations concerning the carcinogenicity of 3,3'-dichlorobenzidine are restricted to

three limited studies in which the health of occupationally exposed individuals was examined (Gerarde & Gerarde, 1974; Gadian, 1975; MacIntyre, 1975). Although no evidence of a relationship between occupational exposure to 3,3'-dichlorobenzidine and an increased incidence of tumours or death due to cancer was reported in these investigations, the available information, owing to the limitations of these studies, is considered inadequate to assess the carcinogenicity of 3,3'-dichlorobenzidine in humans.

Available data were inadequate to assess the non-neoplastic effects of 3,3'-dichlorobenzidine. 3,3'-Dichlorobenzidine has been found to be carcinogenic to rats, mice, dogs, and possibly hamsters (Pliss 1959, 1963; Sellakumar et al., 1969; Stula et al., 1975, 1978; Osanai, 1976). However, it should be noted that all of these studies were limited owing to small group sizes, single dose levels, relatively short periods of exposure, or inadequate histopathological analysis and reporting of data.

In view of the sufficient evidence of the carcinogenicity of 3,3'-dichlorobenzidine in multiple animal species and the substantial evidence of its genotoxicity in bacterial and mammalian cells, both *in vitro* and *in vivo*, 3,3'-dichlorobenzidine is considered to be a genotoxic carcinogen. Carcinogenicity is the critical end-point.

The carcinogenic potency ($TD_{0.05}$), the dose of 3,3'-dichlorobenzidine associated with a 5% increase in tumour incidence, has been characterized based on the increased incidence of mammary tumours (fibroadenomas and adenocarcinomas [combined] in males and females), granulocytic leukaemias (males), and Zymbal gland carcinomas (males) in Chr-CD rats administered 1000 ppm 3,3'-dichlorobenzidine in the diet in the study conducted by Stula et al. (1975). This study was considered most appropriate for quantitative assessment, owing to the size ($n = 50$) of the study groups, which were relatively large compared with those in other available investigations, and to the relative adequacy of documentation of the protocol and results. It should be noted, however, that only one dose level was administered in this study and that the period of administration was less than 2 years (i.e. up to 488 days). A $TD_{0.05}$ was not developed based on tumour incidence in the Osanai (1976) study owing to its limitations, including small group size, use of one sex only, single dose level, relatively short period of follow-up, and inadequate histopathological analysis and reporting of data; however, it would likely be less than that derived from Stula et al. (1975).

Based on the dietary study (50 mg/kg body weight per day) conducted in rats by Stula et al. (1975), the $TD_{0.05}$ calculated based on linear interpolation, incorporating a body weight to surface area correction (power of

2/3, owing to the lack of identification of the active metabolite[s]) and correcting for less than 2 years of exposure, ranges from 0.74 mg/kg body weight per day (based on mammary tumours in females) to 1.4 mg/kg body weight per day (based on granulocytic leukaemias in males).

Available data were inadequate to serve as a basis for developing a $TC_{0.05}$ for inhalation of 3,3'-dichlorobenzidine in air.

11.1.2 Criteria for setting guidance values for 3,3'-dichlorobenzidine

As available data indicate that 3,3'-dichlorobenzidine is a genotoxic carcinogen, exposure should be reduced to the extent possible. The following quantitative guidance is provided as a possible basis for derivation of limits of exposure and judgement of the quality of environmental media by relevant authorities, based on the carcinogenic potency of 3,3'-dichlorobenzidine. Based on very limited available data, the principal medium of exposure to 3,3'-dichlorobenzidine for the general population is unclear, although it is likely to be inhalation and dermal exposure in the occupational environment. Available data are considered inadequate to serve as a basis for the development of tolerable intakes of 3,3'-dichlorobenzidine based on non-neoplastic effects.

Although it is desirable to reduce exposure to genotoxic carcinogens to the extent possible, a value derived by dividing the low end of the $TD_{0.05}$ range (i.e. 0.74 mg/kg body weight per day) by, for example, 5000–50 000 (i.e. 1.48×10^{-4} to 1.48×10^{-5} mg/kg body weight per day) might be considered appropriate as a guidance value for ingested media. This margin affords protection similar to that associated with the range for low-dose risk estimates generally considered by various agencies to be “essentially negligible” (i.e. 10^{-5} to 10^{-6}). The limitations of the critical study (Stula et al., 1975) upon which this guidance value is based should be borne in mind, however, in its interpretation.

Available data are inadequate to serve as a basis for developing a guidance value for 3,3'-dichlorobenzidine in air.

11.1.3 Sample risk characterization

The extremely limited nature of the available data that serve as a basis for estimation of exposure should be borne in mind in interpreting the comparison presented here for indirect population exposure to 3,3'-dichlorobenzidine in the general environment.

Based upon the sample estimates of exposure presented in section 6.2 involving primarily detection limits in monitoring studies in which the compound was not detected or predicted concentrations in Canada, the total daily intake of 3,3'-dichlorobenzidine by the general population via indirect exposure in the general environment is several orders of magnitude less than the sample guidance values derived above. Identified data are inadequate to serve as a basis for estimating exposure to 3,3'-dichlorobenzidine in the occupational environment.

11.2 Evaluation of environmental effects

Owing to its relatively low volatility, very short residence time, and low concentrations in the atmosphere, 3,3'-dichlorobenzidine is not expected to contribute to the greenhouse effect, depletion of the ozone layer, or the formation of ground-level ozone.

The most sensitive aquatic species of those examined, or for which predictions have been made, was bacteria in the Microtox assay, with an IC_{50} value of 0.06 mg/litre. This value is 200 to >240 times greater than measured levels in surface water ($<0.25-0.3$ g/litre) and about 1.8×10^{11} times greater than the concentration predicted in water (3.4×10^{-7} ng/litre) using worst-case assumptions for release in Canada. Similarly, the 96-hour LC_{50} for 3,3'-dichlorobenzidine in the most sensitive fish species (i.e. 0.5 mg/litre in bluegill sunfish) is approximately 1670 to >2000 times greater than measured levels in surface water and about 1.4×10^{12} times greater than the predicted concentration in water. 3,3'-Dichlorobenzidine binds strongly to soil and aquatic sediment and is therefore likely to have reduced bioavailability. Therefore, on the basis of the limited available data, it is likely that 3,3'-dichlorobenzidine poses negligible risk to aquatic organisms.

12. PREVIOUS EVALUATIONS BY INTERNATIONAL BODIES

The International Agency for Research on Cancer has classified 3,3'-dichlorobenzidine in group 2B (“possibly carcinogenic to humans”), based on inadequate evidence for carcinogenicity in humans and sufficient evidence for carcinogenicity in animals (IARC, 1987).

Information on international hazard classification and labelling is included in the International Chemical Safety Card reproduced in this document.

13. HUMAN HEALTH PROTECTION AND EMERGENCY ACTION

Human health hazards, together with preventative and protective measures and first aid recommendations, are presented in the International Chemical Safety Card (ICSC 0481) reproduced in this document.

13.1 Human health hazards

3,3'-Dichlorobenzidine is considered to be a potential human carcinogen. It also has the potential to adversely affect the developing embryo, based upon studies conducted in animals.

13.2 Advice to physicians

In case of poisoning, treatment is supportive. Special attention should be given to pregnant women exposed to 3,3'-dichlorobenzidine.

13.3 Health surveillance advice

Workers potentially exposed to 3,3'-dichlorobenzidine should undergo regular urine cytology surveillance. This should be followed by more specific procedures in the case of positive results and should be included in the health surveillance programme in parallel with the monitoring of liver function.

13.4 Fire hazards

3,3'-Dichlorobenzidine is combustible; toxic gases (hydrogen chloride, nitrogen oxides) may be produced in a fire.

13.5 Spillage and disposal

13.5.1 Spillage

In the event of spillage, measures should be taken to prevent 3,3'-dichlorobenzidine from reaching drains or watercourses, owing to potential bioaccumulation and toxicity in aquatic species.

13.5.2 Disposal

Disposal of contaminated waste is achieved by high-temperature incineration with hydrochloric acid scrubber or microwave plasma detoxification.

14. CURRENT REGULATIONS, GUIDELINES, AND STANDARDS

Information on national regulations, guidelines, and standards is available from the International Register of Potentially Toxic Chemicals (IRPTC) legal file. The reader should be aware that regulatory decisions about chemicals taken in a certain country can be fully understood only in the framework of the legislation of that country. The regulations and guidelines of all countries are subject to change and should always be verified with appropriate regulatory authorities before application.

3,3'-DICHLOROBENZIDINE**0481**

April 1994

CAS No: 91-94-1

RTECS No: DD0525000

UN No:

EC No: 612-068-00-4

3,3'-Dichlorobiphenyl-4,4'-ylenediamine

4,4'-Diamino-3,3'-dichlorobiphenyl

 $C_6H_3Cl_2NH_2C_6Cl_2NH_2 / C_{12}H_{10}Cl_2N_2$

Molecular mass: 253.1

TYPES OF HAZARD/ EXPOSURE	ACUTE HAZARDS/SYMPTOMS	PREVENTION	FIRST AID/FIRE FIGHTING
FIRE	Combustible. Gives off irritating or toxic fumes (or gases) in a fire.	NO open flames.	Powder, water spray, foam, carbon dioxide.
EXPLOSION			

EXPOSURE		PREVENT DISPERSION OF DUST! PREVENT GENERATION OF MISTS! AVOID ALL CONTACT!	IN ALL CASES CONSULT A DOCTOR!
Inhalation	Cough. Sore throat.	Avoid inhalation of fine dust and mist. Local exhaust or breathing protection.	Fresh air, rest. Refer for medical attention.
Skin	MAY BE ABSORBED!	Protective gloves. Protective clothing.	Remove contaminated clothes. Rinse and then wash skin with water and soap. Refer for medical attention.
Eyes		Face shield or eye protection in combination with breathing protection if powder.	First rinse with plenty of water for several minutes (remove contact lenses if easily possible), then take to a doctor.
Ingestion		Do not eat, drink, or smoke during work. Wash hands before eating.	Rinse mouth. Refer for medical attention.

SPILLAGE DISPOSAL

Sweep spilled substance into sealable containers; if appropriate, moisten first to prevent dusting. Carefully collect remainder, then remove to safe place. Do NOT let this chemical enter the environment (extra personal protection: complete protective clothing including self-contained breathing apparatus).

PACKAGING & LABELLING

T Symbol
R: 45-21-43
S: 53-45
Note: E

Do not transport with food and feedstuffs.

EMERGENCY RESPONSE

Transport Emergency Card: TEC (R)-61G12b

STORAGE

Separated from food and feedstuffs. Well closed.

IPCS

International
Programme on
Chemical Safety



Prepared in the context of cooperation between the International Programme on Chemical Safety and the European Commission
© IPCS 1999

SEE IMPORTANT INFORMATION ON THE BACK.

IMPORTANT DATA

Physical State; Appearance

GREY TO PURPLE CRYSTALS.

Chemical Dangers

The substance decomposes on heating producing toxic and corrosive fumes including nitrogen oxides and hydrogen chloride.

Occupational Exposure Limits

TLV: ppm; mg/m³ A2 (skin) (ACGIH 1993-1994).

Routes of Exposure

The substance can be absorbed into the body by inhalation of its aerosol, through the skin and by ingestion.

Inhalation Risk

Evaporation at 20°C is negligible; a harmful concentration of airborne particles can, however, be reached quickly when dispersed, especially if powdered.

Effects of Short-term Exposure

The substance irritates the respiratory tract.

Effects of Long-term or Repeated Exposure

Repeated or prolonged contact with skin may cause dermatitis. The substance may have effects on the liver. This substance is probably carcinogenic to humans.

PHYSICAL PROPERTIES

Boiling point: 368°C

Melting point: 132-133°C

Solubility in water: none

Auto-ignition temperature: 350°C

ENVIRONMENTAL DATA

The substance is toxic to aquatic organisms.

NOTES

The substance is combustible but no flash point is available in literature. Curithane C126 is a trade name.

ADDITIONAL INFORMATION

LEGAL NOTICE

Neither the EC nor the IPCS nor any person acting on behalf of the EC or the IPCS is responsible for the use which might be made of this information

REFERENCES

- ACGIH (1991) 3,3'-Dichlorobenzidine. In: *Documentation of the threshold limit values and biological exposure indices*, 6th ed. Cincinnati, OH, American Conference of Governmental Industrial Hygienists, pp. 417–419.
- Anderson D, Styles J (1978) The bacterial mutation test. *British journal of cancer*, 37:924–930.
- Appleton H, Sikka H (1980) Accumulation, elimination and metabolism of dichlorobenzidine in the bluegill sunfish. *Environmental science and technology*, 14:50–54.
- Ashby J, Mohammed R (1988) UDS activity in the rat liver of the human carcinogens benzidine and 4-aminobiphenyl, and the rodent carcinogens 3,3'-dichlorobenzidine and Direct Black 38. *Mutagenesis*, 3:69–71.
- ATSDR (1989) *Toxicological profile for 3,3'-dichlorobenzidine*. Atlanta, GA, US Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry (PB90-168691).
- Banerjee S, Sikka H, Gary R, Kelly C (1978) Photodegradation of 3,3'-dichlorobenzidine. *Environmental science and technology*, 12:1425–1427.
- BUA (1993) 3,3'-Dichlorobenzidine. GDCh-Advisory Committee on Existing Chemicals of Environmental Relevance, March 1989. New York, NY, VCH Publishers, Inc. (BUA Report No. 30).
- Chemicals Daily (1993) 12493 chemical products. Chemicals Daily Co., Ltd., p. 751.
- Chemicals Daily (1994) 12394 chemical products. Chemicals Daily Co., Ltd., p. 767.
- Cihak R, Vontorkova M (1987) Benzidine and 3,3'-dichlorobenzidine (DCB) induce micronuclei in the bone marrow and the fetal liver of mice after gavage. *Mutagenesis*, 2:267–269.
- Dutka B, Kwan K (1981) Comparison of three microbial toxicity screening tests with the Microtox test. *Bulletin of environmental contamination and toxicology*, 27:753–757.
- Freeman A, Weisburger E, Weisburger J, Wolford R, Maryak J, Huebner R (1973) Transformation of cell cultures as an indication of the carcinogenic potential of chemicals. *Journal of the National Cancer Institute*, 51:799–808.
- Freitag D, Ballhorn L, Geyer H, Korte F (1985) Environmental hazard profile for organic chemicals. An experimental method for the assessment of the behaviour of organic chemicals in the ecosystem by means of simple laboratory tests with ¹⁴C-labelled chemicals. *Chemosphere*, 14:1589–1616.
- Fricke C, Clarkson C, Lomnitz E, O'Farrell T (1985) Comparing priority pollutants in municipal sludges. *Biocycle*, 26:35–37.
- Gadian T (1975) Carcinogens in industry, with special reference to dichlorobenzidine. *Chemistry & Industry (London)*, 4:821–831.
- Garner R, Walpole A, Rose F (1975) Testing of some benzidine analogues for microsomal activation to bacterial mutagens. *Cancer letters*, 1:39–42.
- Gerarde H, Gerarde D (1974) Industrial experience with 3,3'-dichlorobenzidine: an epidemiology study of a chemical manufacturing plant. *Journal of occupational medicine*, 16:322–344.
- Ghosal A, Iba M (1992) Enhancement of butylated hydroxytoluene of the *in vitro* activation of 3,3'-dichlorobenzidine. *Mutation research*, 278:31–41.
- Golub N, Kolesnichenko T, Shabad L (1975) [Oncogenic action of some nitrogen compounds on the progeny of experimental mice.] *Bulletin of experimental biology and medicine*, 78:1402–1404 (in Russian) [cited in US EPA (1988) *Health and environmental effects document for 3,3'-dichlorobenzidine*. Washington, DC, US Environmental Protection Agency, Environmental Criteria and Assessment Office (ECAO-CIN-G034)].
- Government of Canada (1993) *Canadian Environmental Protection Act. Priority Substances List assessment report for 3,3'-dichlorobenzidine*. Prepared by Health Canada and Environment Canada. Ottawa, Ontario, Canada Communication Group Publishing (ISBN 0-662-21070-9).
- Howard P, Boethling R, Jarvis W, Meylan W, Michalenk E (1991) *Handbook of environmental degradation rates*. Chelsea, MI, Lewis Publishers, Inc.
- HSDB (1995) *Data profile for 3,3'-dichlorobenzidine*. Hamilton, Ontario, Canadian Centre for Occupational Health and Safety, Hazardous Substances Databank.
- IARC (1982) 3,3'-Dichlorobenzidine and its dihydrochloride. Lyon, International Agency for Research on Cancer, pp. 239–256 (IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man, Vol. 29).
- IARC (1987) 3,3'-Dichlorobenzidine (Group 2B). Lyon, International Agency for Research on Cancer, pp. 193–194 (IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man, Suppl. 7).
- Iba M (1987) Comparative activation of 3,3'-dichlorobenzidine and related benzidines to mutagens in *Salmonella typhimurium* assays by hepatic S9 and microsomes from rats pretreated with different inducers of cytochrome P-450. *Mutation research*, 182:231–241.
- IPCS (1993) *International Chemical Safety Card — 3,3'-Dichlorobenzidine*. Geneva, World Health Organization, International Programme on Chemical Safety (No. 0481).
- IPCS (1994) *Assessing human health risks of chemicals: derivation of guidance values for health-based exposure limits*. Geneva, World Health Organization, International Programme on Chemical Safety (Environmental Health Criteria 170).
- Law R (1995) 3,3'-Dichlorobenzidine: a candidate for inclusion in marine monitoring programmes? *Chemosphere* 30:1791–1797.
- Lazear E, Shaddock J, Barren P, Louie S (1979) The mutagenicity of some of the proposed metabolites of Direct Black 38 and Pigment Yellow 12 in the *Salmonella typhimurium* assay system. *Toxicology letters*, 4:519–525.
- MacIntyre I (1975) Experience of tumours in a British plant handling 3,3'-dichlorobenzidine. *Journal of occupational medicine*, 17:23–26.
- Mackay D, Paterson S (1991) Evaluating the multimedia fate of organic chemicals: a level III fugacity model. *Environmental science and technology*, 25:427–436.
- Malaiyandi M, Wightman R, LaFerriere C (1987) Concentration of selected organic pollutants: comparison of adsorption and reverse osmosis techniques. In: Malaiyandi M, ed. *Organic pollutants in water. Sampling, analysis and toxicity testing*. Washington, DC, American Chemical Society, pp. 163–179 (American Chemical Society Symposium Series No. 214).
- Martin C, McDermid A, Garner R (1978) Testing of known carcinogens and noncarcinogens for their ability to induce unscheduled DNA synthesis. *Cancer research*, 38:2621–2627.
- Messerly E, Fekete J, Wade D, Sinsheimer J (1987) Structure–mutagenicity relationships of benzidine analogues. *Environmental and molecular mutagenesis*, 10:263–274.
- Narang A, Choudhury D, Richards A (1982) Separation of aromatic amines by thin-layer and high performance liquid chromatography. *Journal of chromatographic science*, 20:235–237.

- Osanai H (1976) [An experimental study on hepatoma caused by aromatic amines.] *Journal of science of labour*, 52:179–201 (in Japanese).
- Pliss G (1959) [Dichlorobenzidine as a blastomogenic agent.] *Voprosy Onkologii*, 5:524–533 (in Russian).
- Pliss G (1963) On some regular relationships between carcinogenicity of aminodiphenyl derivatives and the structure of substances. *Acta Unio Internationalis Contra Cancrum*, 19:499–501.
- Reid T, Wang C, King C, Morton K (1984) Mutagenicity of some benzidine congeners and their *N*-acetylated and *N,N*-diacetylated derivatives in different strains of *Salmonella typhimurium*. *Environmental mutagenesis*, 6:145–151.
- Riggin R, Howard C, Scott D, Hedgecote R (1983) Determination of benzidine related congeners and pigments in atmospheric particulate matter. *Journal of chromatography*, 27:321–325.
- Saffiotti U, Cefis F, Montessano R, Sellakumar A (1967) Induction of bladder cancer in hamsters fed aromatic amines. In: Deichman W, Lampe K, eds. *Bladder cancer*. Birmingham, AL, Aesculapis Publishing Co., pp. 129–135.
- Savard S, Josephy P (1986) Synthesis and mutagenicity of 3,3'-dihalogenated benzidines. *Carcinogenesis*, 7:1239–1241.
- Sellakumar A, Montesano R, Saffiotti U (1969) Aromatic amines: carcinogenicity in hamsters. *Proceedings of the American Association for Cancer Research*, 10:78 (abstract).
- Shabad L, Sorokina J, Golub N, Bogovski S (1972) Transplacental effect of some chemical compounds on organ cultures of embryonic tissue. *Cancer research*, 32:617–627.
- Shiraishi Y (1986) Hypersensitive character of Bloom syndrome B-lymphoblastoid cell lines usable for sensitive carcinogen detection. *Mutation research*, 175:179–187.
- Sikka H, Appleton H, Banerjee S (1978) *Fate of 3,3'-dichlorobenzidine in aquatic environments*. Athens, GA, US Environmental Protection Agency, Environmental Research Laboratory (EPA 600/3-78-068).
- Slobodnik J, Groenewegen M, Brouwer E, Lingeman H, Brinkman U (1993) Fully automated multi-residue method for trace level monitoring of polar pesticides by liquid chromatography. *Journal of chromatography*, 642:359–370.
- Smith E, Weber W (1990) Comparative assessment of the chemical and adsorptive characteristics of leachates from a municipal and an industrial landfill. *Water, air, and soil pollution*, 53:279–295.
- Staples C, Werner A, Hoogheem T (1985) Assessment of priority pollutant concentrations in the United States using STORET database. *Environmental toxicology and chemistry*, 4:131–142.
- Stula E, Sherman H, Zapp J, Clayton J (1975) Experimental neoplasia in rats from oral administration of 3,3'-dichlorobenzidine, 4,4'-methylene-bis(2-chloroaniline), and 4,4'-methylene-bis(2-methylaniline). *Toxicology and applied pharmacology*, 31:159–176.
- Stula E, Barnes J, Sherman H, Reinhardt C, Zapp J (1978) Liver and urinary bladder tumours in dogs from 3,3'-dichlorobenzidine. *Journal of environmental pathology and toxicology*, 1:475–490.
- Tsuda H, Miyata Y, Murasaki G, Kinoshita H, Fukushima S, Ito N (1977) Synergistic effect of urinary bladder carcinogenesis in rats treated with *N*-butyl-*N*-(4-hydroxybutyl)nitrosamine, *N*-[4-(5-nitro-2-furyl)-2-thiazolyl]formamide, *N*-2-fluorenylacetamide and 3,3'-dichlorobenzidine. *Gann*, 68:183–192.
- US DHHS (1994) *Seventh annual report on carcinogens. Summary 1994*. Research Triangle Park, NC, US Department of Health and Human Services, Public Health Service, National Institutes of Health, National Institute of Environmental Health Sciences.
- US EPA (1980) *Ambient water quality criteria for dichlorobenzidine*. Washington, DC, US Environmental Protection Agency, Office of Water Regulations and Standards (PB81-117517).
- US EPA (1990a) *Remedial investigation report, landfill area, Greenville, South Carolina*. Washington, DC, US Environmental Protection Agency, Office of Toxic Substances (Document No. 86-900000412).
- US EPA (1990b) *Subsurface investigation, Glenholden Laboratory, Glenholden, Pennsylvania*. Washington, DC, US Environmental Protection Agency, Office of Toxic Substances (Document No. 86-910000001).
- US EPA (1990c) *Letter from PMS Consolidated to USEPA containing information on study of potential workplace exposure to 3,3'-dichlorobenzidine, with attachment*. Washington, DC, US Environmental Protection Agency, Office of Toxic Substances (Document No. 89-900000363).
- Valls M, Bayona J, Albaigés J (1990) Broad spectrum analysis of ionic and non-ionic organic contaminants in urban wastewaters and coastal receiving aquatic systems. *International journal of environmental analytical chemistry*, 39:329–348.
- You Z, Brezzell M, Das S, Espadas-Torre M, Hooberman B, Sinsheimer J (1993) *Ortho*-substituent effects on the *in vitro* and *in vivo* genotoxicity of benzidine derivatives. *Mutation research*, 319:19–30.

APPENDIX 1 — SOURCE DOCUMENTS

Government of Canada (1993)

Copies of the *Canadian Environmental Protection Act (CEPA) Priority Substances List assessment report for 3,3'-dichlorobenzidine* (Government of Canada, 1993) may be obtained from the:

Commercial Chemicals Branch
Environment Canada
14th Floor, Place Vincent Massey
351 St. Joseph Blvd.
Hull, Quebec
Canada K1A 0H3

Environmental Health Centre
Health Canada
Address Locator: 0801A
Tunney's Pasture
Ottawa, Ontario
Canada K1A 0L2

Copies of the unpublished Supporting Documentation related to human health effects that formed the basis for preparation of the above-mentioned report may be obtained from the Environmental Health Centre at the address noted above. Copies of the unpublished Supporting Documentation related to effects on the environment that formed the basis for preparation of the above-mentioned report may be obtained from the Commercial Chemicals Branch at the address noted above.

Initial drafts of the Supporting Documentation and Assessment Report for 3,3'-dichlorobenzidine were prepared by staff of Health Canada and Environment Canada. The environmental sections were reviewed by Drs C.M. Auer and W.H. Farland of the US Environmental Protection Agency. Sections related to the assessment of human health effects were approved by an inter-directorate Standards and Guidelines Rulings Committee of the Bureau of Chemical Hazards of Health Canada. The final Assessment Report was reviewed and approved by the Environment Canada/Health Canada CEPA Management Committee.

Agency for Toxic Substances and Disease Registry (1989)

Copies of the ATSDR *Toxicological profile for 3,3'-dichlorobenzidine* (ATSDR, 1989) may be obtained from the:

Agency for Toxic Substances and Disease Registry
Division of Toxicology
1600 Clifton Road, E-29
Atlanta, Georgia 30333
USA

Initial drafts of the *Toxicological profile for 3,3'-dichlorobenzidine* were reviewed by scientists from the Agency for Toxic Substances and Disease Registry, the US Environmental Protection Agency, the US Centre for Disease Control and Prevention, and the US National Toxicology Program. The document was also reviewed by an expert panel of non-governmental reviewers, consisting of the following members: Dr Paul Mushak, Private Consultant, Durham, North Carolina; Dr David Jollow, Professor, Medical University of South Carolina; and Dr T. Kneip, Professor, New York University Medical Center.

APPENDIX 2 — CICAD PEER REVIEW

The draft CICAD on 3,3'-dichlorobenzidine was sent for review to institutions and organizations identified by IPCS after contact with IPCS national Contact Points and Participating Institutions, as well as to identified experts. Comments were received from:

Department of Health, London, United Kingdom

Department of Public Health, Albert Szent-Gyorgyi University Medical School, Szeged, Hungary

Dirección General de Salud Ambiental, Subsecretario de Regulación y Fomento Sanitario, San Luis Potosí, Mexico

Fraunhofer Institute of Toxicology and Aerosol Research, Hanover, Germany

Guy's & St. Thomas' Hospital Trust, Medical Toxicology Unit, London, United Kingdom

Health and Safety Executive, Bootle, United Kingdom

Hoechst Aktiengesellschaft, Frankfurt, Germany

International Agency for Research on Cancer, Lyon, France

Ministry of Health, National Centre of Hygiene, Medical Ecology and Nutrition, Sofia, Bulgaria

Ministry of Health and Welfare, International Affairs Division, Government of Japan, Tokyo, Japan

National Institute for Working Life, Solna, Sweden

United States Department of Health and Human Services (Agency for Toxic Substances and Disease Registry; National Institute of Environmental Health Sciences)

United States Environmental Protection Agency (Office of Pollution Prevention and Toxics; National Center for Environmental Assessment, Office of Research and Development; Office of Drinking Water)

APPENDIX 3 — CICAD FINAL REVIEW BOARD

Brussels, Belgium, 18–20 November 1996

Members

Dr A. Aitio, Institute of Occupational Health, Helsinki, Finland

Dr K. Bentley, Director, Environment Policy Section, Commonwealth Department of Human Services and Health, Canberra, Australia

Mr R. Cary, Toxicology and Existing Substances Regulation Unit, Health and Safety Executive, Merseyside, United Kingdom

Dr J. de Fouw, National Institute of Public Health and Environmental Protection, Bilthoven, The Netherlands

Dr C. DeRosa, Director, Division of Toxicology, Agency for Toxic Substances and Disease Registry, Atlanta, GA, USA

Dr S. Dobson, Institute of Terrestrial Ecology, Monks Wood, Abbots Ripton, Huntingdon, Cambridgeshire, United Kingdom

Dr W. Farland, Director, National Center for Environmental Assessment, Office of Research and Development, US Environmental Protection Agency, Washington, DC, USA (*Chairperson*)

Dr T.I. Fortoul, Depto. Biología Celular y Tisular, National University of Mexico and Environmental Health Directorate of the Health Ministry, Mexico D.F., Mexico

Dr H. Gibb, National Center for Environmental Assessment, US Environmental Protection Agency, Washington, DC, USA

Dr R.F. Hertel, Federal Institute for Health Protection of Consumers & Veterinary Medicine, Berlin, Germany

Mr J.R. Hickman, Environmental Health Directorate, Health Canada, Ottawa, Ontario, Canada

Dr T. Lakhanisky, Head, Division of Toxicology, Institute of Hygiene and Epidemiology, Brussels, Belgium (*Vice-Chairperson*)

Dr I. Mangelsdorf, Documentation and Assessment of Chemicals, Fraunhofer Institute for Toxicology and Aerosol Sciences, Hanover, Germany

Ms E. Meek, Head, Priority Substances Section, Environmental Health Directorate, Health Canada, Ottawa, Ontario, Canada

Dr K. Paksy, National Institute of Occupational Health, Budapest, Hungary

Mr D. Renshaw, Department of Health, London, United Kingdom

Dr J. Sekizawa, Division of Chemo-Bio Informatics, National Institute of Hygienic Sciences, Tokyo, Japan

Dr H. Sterzl-Eckert, GSF-Forschungszentrum für Umwelt und Gesundheit GmbH, Institut für Toxikologie, Oberschleissheim, Germany

Professor S. Tarkowski, Department of Environmental Health Hazards, The Nofer Institute of Occupational Medicine, Lodz, Poland

Dr M. Wallen, National Chemicals Inspectorate (KEMI), Solna, Sweden

Observers

Professor F.M.C. Carpanini,¹ Director, Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC), Brussels, Belgium

Mr R. Haigh,¹ Head of Unit, Health and Safety Directorate, European Commission, Luxembourg

Mr B.U. Hildebrandt, Federal Ministry for the Environment, Nature Conservation and Nuclear Safety, Bonn, Germany

Mr P. Hurst,¹ Chemical and Consumer Policy Officer, Conservation Policy Division, World Wide Fund for Nature, Gland, Switzerland

Dr A. Lombard (Representative of CEFIC), ELF-ATOCHEM, Paris, France

Dr P. McCutcheon,¹ Environment, Consumer Protection and Nuclear Safety, European Commission, Brussels, Belgium

Dr R. Montaigne, Counsellor, Technical Affairs Department, European Chemical Industry Council (CEFIC), Brussels, Belgium

Dr M. Pemberton, ICI Acrylics, Lancashire, United Kingdom

Dr A. Smith, Organisation for Economic Co-operation and Development, Environment Division, Paris, France

Secretariat

Dr M. Baril, International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland

Dr L. Harrison, International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland

Dr M. Mercier, Director, International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland

Dr P. Toft, Associate Director, International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland

¹ Invited but unable to attend.

RÉSUMÉ D'ORIENTATION

La Direction de l'Hygiène du Milieu de Santé Canada a rédigé ce CICAD (Document international succinct sur l'évaluation des risques chimiques) sur la 3,3'-dichlorobenzidine en s'inspirant principalement des évaluations du Gouvernement du Canada (1993) et de l'Agency for Toxic Substances and Disease Registry (ATSDR, 1989) visant à déterminer les effets potentiels sur la santé humaine d'une exposition indirecte à la 3,3'-dichlorobenzidine dans l'environnement général, ainsi que les effets de cette substance sur l'environnement. L'évaluation du Gouvernement du Canada (1993) a pris en compte les données relatives à la détermination des effets de la 3,3'-dichlorobenzidine sur l'environnement et la santé humaine qui étaient disponibles en avril 1992 (effets sur l'environnement) et en octobre 1992 (effets sur la santé humaine); ces données ont été mises à jour en septembre 1995 à partir des données du Registre international des substances chimiques potentiellement toxiques et de bases de données en ligne. Des informations concernant la nature de l'évaluation par les pairs et la disponibilité des documents du Gouvernement du Canada (1993) et de l'ATSDR (1989) figurent à l'appendice 1. Des informations sur l'évaluation par les pairs du présent CICAD figurent à l'appendice 2. Ce CICAD a été approuvé pour publication à une réunion du Comité d'évaluation finale qui s'est tenue à Bruxelles (Belgique) du 18 au 20 novembre 1996. La liste des participants à la réunion du Comité d'évaluation finale figure à l'appendice 3. La fiche d'information sur la sécurité chimique (ICSC 0481) pour la 3,3'-dichlorobenzidine, préparée par le Programme international sur la sécurité chimique (IPCS, 1993), est également reproduite dans le présent document.

La 3,3'-dichlorobenzidine (CAS N°/ 91-94-1) est une amine aromatique primaire chlorée synthétique disponible dans le commerce sous la forme de dichlorhydrate de 3,3'-dichlorobenzidine ($C_{12}H_{10}N_2Cl_2 \cdot 2HCl$). La 3,3'-dichlorobenzidine et certains de ses dérivés sont utilisés principalement comme intermédiaires dans la fabrication de pigments pour les encres d'imprimerie, les textiles, les peintures et les matières plastiques. Elle est également utilisée pour le titrage de l'or et comme agent de polymérisation dans la synthèse d'élastomères de la famille des polyuréthanes.

L'exposition professionnelle à la 3,3'-dichlorobenzidine est possible lors de la fabrication de pigments et dans les installations industrielles où des pigments qui en contiennent sont chauffés pendant des périodes prolongées. Des concentrations de 3,3'-dichlorobenzidine comprises entre #0,6 à 25 : g/m^3 ont été mesurées dans l'air des ateliers de production et des usines de fabrication de pigments en Allemagne et au Japon.

Étant donné sa volatilité relativement faible, sa très courte persistance et sa faible concentration dans l'atmosphère, la 3,3'-dichlorobenzidine ne devrait pas contribuer à l'effet de serre, à la destruction de la couche d'ozone ou à la formation d'ozone au niveau du sol. D'après les données disponibles, il est probable que la 3,3'-dichlorobenzidine présente un risque négligeable pour les organismes aquatiques.

Les données disponibles sont insuffisantes pour établir des doses tolérables de 3,3'-dichlorobenzidine fondées sur ses effets non néoplasiques. Des études limitées ont apporté des preuves suffisantes de sa cancérogénicité chez de nombreuses espèces animales et sa génotoxicité a été démontrée *in vitro* et *in vivo*; en conséquence, la 3,3'-dichlorobenzidine est considérée comme une substance potentiellement cancérigène pour l'homme. Compte tenu de cette cancérogénicité potentielle et de l'absence de données épidémiologiques adéquates, une valeur guide fondée sur des critères de santé peut être établie sur la base du potentiel cancérigène (c'est-à-dire sur la $DT_{0,05}$) déterminé à partir des données de la mieux présentée des études de toxicité chronique. Dans cette étude, certes limitée, des rats ChR-CD ont consommé pendant 488 jours une nourriture contenant 1000 ppm de 3,3'-dichlorobenzidine. La $DT_{0,05}$ a été calculée par interpolation linéaire en incorporant un facteur de correction du poids corporel en fonction de la surface corporelle (puissance 2/3 en raison de l'absence d'identification du ou des métabolites actifs) et un autre facteur tenant compte de la durée d'exposition inférieure à deux ans. La fourchette obtenue a été de 0,74 à 1,4 mg/kg de poids corporel par jour. En divisant la valeur inférieure de cette fourchette (soit 0,74 mg/kg de poids corporel par jour) par 5000 – 50 000, on obtient $1,48 \times 10^{-4}$ à $1,48 \times 10^{-5}$ mg/kg de poids corporel par jour, ce qui peut être considéré comme une valeur guide appropriée pour l'ingestion. Cette marge offre une protection analogue à celle des fourchettes d'exposition aux faibles doses qui sont généralement considérées par les organismes compétents comme présentant un risque "pratiquement négligeable" (soit 10^{-5} à 10^{-6}). Si l'on se base sur une estimation de l'exposition effectuée à partir des concentrations prédites ou des quelques données recueillies aux États-Unis d'Amérique et au Canada, où la substance n'a généralement pas été détectée, la dose quotidienne totale estimative absorbée par la population générale (des suites d'une exposition indirecte à l'environnement général) est inférieure de plusieurs ordres de grandeur à la valeur guide indiquée ci-dessus.

RESUMEN DE ORIENTACIÓN

Esta reseña de la evaluación química internacional de la 3,3'-diclorobencidina fue preparada por la Dirección de Higiene del Medio de Health Canada, principalmente sobre la base de revisiones del Gobierno del Canadá (1993) y de la Agencia para el Registro de Sustancias Tóxicas y Enfermedades (ATSDR, 1989), a fin de evaluar los efectos potenciales en la salud humana de la exposición indirecta a la 3,3'-diclorobencidina en el medio ambiente general, así como sus efectos ambientales. En su estudio (1993), el Gobierno del Canadá examinó los datos pertinentes para la evaluación de los efectos de la 3,3'-diclorobencidina en el medio ambiente y la salud humana identificados hasta abril de 1992 (efectos ambientales) y octubre de 1992 (efectos en la salud humana). Posteriormente los datos se actualizaron hasta septiembre de 1995 utilizando el Registro Internacional de Sustancias Químicas Potencialmente Tóxicas y bases de datos en línea. En el apéndice 1 se presenta información sobre el carácter de la revisión científica y la disponibilidad de los documentos del Gobierno del Canadá (1993) y del ATSDR (1989). En el apéndice 2 se presenta información sobre la revisión científica de esta reseña. Esta reseña fue aprobada para publicación en una reunión de la Junta de Revisión Final celebrada en Bruselas, Bélgica, del 18 al 20 de noviembre de 1996. En el apéndice 3 figuran los participantes en dicha reunión. En el presente documento también se reproduce la Ficha Internacional de Seguridad Química (ICSC 0481) de la 3,3'-diclorobencidina, producida por el Programa Internacional de Seguridad de las Sustancias Químicas (IPCS, 1993).

La 3,3'-diclorobencidina (CAS N° 91-94-1) es una amina aromática primaria clorada sintética que se puede obtener comercialmente en forma de sal del dihidrocloruro, dihidrocloruro de 3,3'-diclorobencidina ($C_{12}H_{10}N_2Cl_2 \cdot 2HCl$). La 3,3'-diclorobencidina (y algunos de sus derivados) se utiliza principalmente como intermediario en la fabricación de pigmentos para tintas de imprenta, textiles, pinturas y plásticos. También se utiliza en la determinación analítica del oro y como agente de curado en la síntesis de elastómeros de poliuretano.

La exposición ocupacional a la 3,3'-diclorobencidina puede presentarse en la industria productora de pigmentos y en aplicaciones industriales en las que los pigmentos a base de 3,3'-diclorobencidina se calientan durante periodos prolongados. Se han detectado niveles de 3,3'-diclorobencidina que oscilaban entre #0,6 a 25 : g/m^3 en el aire ambiente de las plantas de producción y plantas de fabricación de pigmentos en Alemania y el Japón.

Debido a su baja volatilidad relativa, persistencia muy breve y baja concentración en la atmósfera, no se cree que la 3,3'-diclorobencidina contribuya al efecto de invernadero, al agotamiento de la capa de ozono ni a la formación de ozono troposférico. Los datos disponibles indican que la 3,3'-diclorobencidina probablemente constituya un riesgo insignificante para los organismos acuáticos.

Los datos disponibles son insuficientes para establecer ingestas tolerables de 3,3'-diclorobencidina en función de los efectos no neoplásicos. Sobre la base de indicios suficientes de carcinogenicidad de la 3,3'-diclorobencidina en múltiples especies animales en estudios limitados e indicios sustanciales de genotoxicidad tanto *in vitro* como *in vivo*, se considera que la 3,3'-diclorobencidina es un posible carcinógeno humano. En vista de su carcinogenicidad potencial para el ser humano y a falta de suficientes datos epidemiológicos, sobre la base del potencial carcinogénico de la 3,3'-diclorobencidina se ha derivado un valor de orientación para la salud ($DT_{0,05}$), calculado a partir de los mejores estudios crónicos notificados, si bien limitados, en los que se alimentó a ratas ChR-CD con 1000 ppm de 3,3'-diclorobencidina en la dieta durante un máximo de 488 días. La $DT_{0,05}$ se calculó sobre la base de una interpolación lineal que incorporaba una corrección del peso respecto de la superficie corporal (potencia de 2/3, debido a la falta de identificación de metabolitos activos) y una corrección por menos de dos años de exposición, con márgenes de variación de 0,74 a 1,4 mg/kg de peso corporal por día. Para obtener un valor de orientación respecto de los medios ingeridos se podría dividir el extremo menor de este margen de $DT_{0,05}$ (es decir, 0,74 mg/kg de peso corporal por día), por ejemplo por 5000–50 000 (es decir, $1,48 \times 10^{-4}$ a $1,48 \times 10^{-5}$ mg/kg de peso corporal por día). Este margen permite una protección semejante a la asociada con el margen correspondiente a las estimaciones de riesgo de dosis bajas generalmente considerados por diversos organismos como «esencialmente insignificantes» (es decir, 10^{-5} a 10^{-6}). Sobre la base de una estimación de muestra de la exposición que comportaba concentraciones previstas o datos de vigilancia limitados procedentes de los Estados Unidos de América y del Canadá, donde en general no se ha detectado esta sustancia química, la ingesta diaria total estimada de 3,3'-diclorobencidina por la población general (por exposición indirecta a través del medio ambiente) es varios órdenes de magnitud inferior al valor de orientación de muestra derivado más arriba.