Concise International Chemical Assessment Document 16

AZODICARBONAMIDE

First draft prepared by
Mr R. Cary, Health and Safety Executive, Merseyside, United Kingdom,
Dr S. Dobson, Institute of Terrestrial Ecology, Cambridgeshire, United Kingdom, and
Mrs E. Ball, Health and Safety Executive, Merseyside, United Kingdom

Please note that the layout and pagination of thispdf file are not identical to those of 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, 1999

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, the United Nations Institute for Training and Research, 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

Azodicarbonamide.

(Concise international chemical assessment document ; 16)

1.Azo compounds 2.Occupational exposure 3.Risk assessment
I.International Programme on Chemical Safety II.Series

ISBN 92 4 153016 2 (NLM classification: QV 235)
ISSN 1020-6167

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

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 undergo 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 170[1] for advice on the derivation of health-based guidance values.

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 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 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.

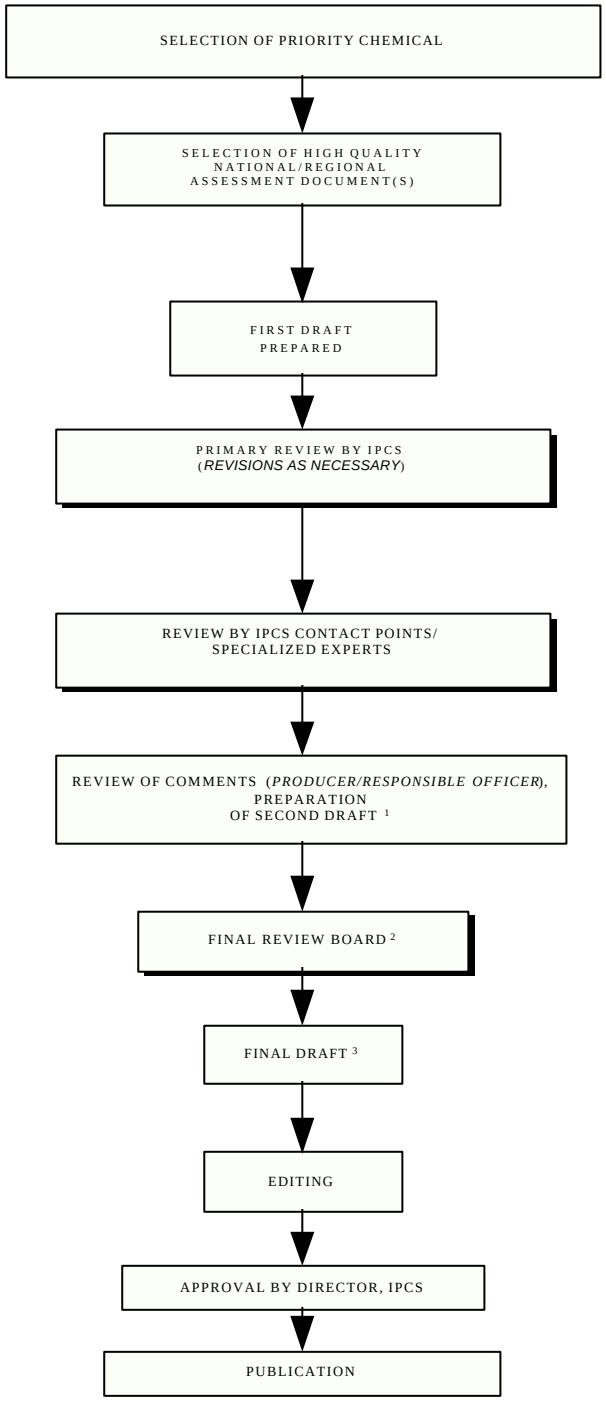
The CICAD Final Review Board has several important functions:

- 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.

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

[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).

CICAD PREPARATION FLOW CHART



1 Taking into account the comments from reviewers.
2 The second draft of documents is submitted to the Final Review Board together with the reviewers' comments.
3 Includes any revisions requested by the Final Review Board.

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 azodicarbonamide was based on a review of human health (primarily occupational) concerns prepared by the United Kingdom's Health and Safety Executive (Ball et al., 1996). Hence, although this CICAD includes an assessment of the available environmental data, the main focus is on risks to human health in the working environment, including an emphasis on information from routes that are relevant to occupational settings. Data identified up to June 1994 were covered in the review. A further literature search was performed, up to July 1997, to identify any new information published since this review was completed. The original source document did not address environmental concerns; as literature searches have failed to identify relevant studies in this area, an environmental risk assessment has not been attempted. Information on the nature of the peer review and availability of the source document is presented in Appendix 1. Information on the peer review of this CICAD is presented in Appendix 2. This CICAD was approved as an international assessment at a meeting of the Final Review Board, held in Tokyo, Japan, on 30 June – 2 July 1998. Participants at the Final Review Board meeting are listed in Appendix 3. The International Chemical Safety Card (ICSC 0380) for azodicarbonamide, produced by the International Programme on Chemical Safety (IPCS, 1993), has also been reproduced in this document.

Toxicokinetic data on azodicarbonamide (CAS No. 123-77-3) are limited, but the chemical appears to be well absorbed by the inhalation and oral routes in rodents. Substantial quantities of the substance remain unabsorbed from the gastrointestinal tract and are passed out in the faeces. Azodicarbonamide is readily converted to biurea, the only breakdown product identified, and it is likely that systemic exposure is principally to this derivative rather than to the parent compound. Elimination of absorbed azodicarbonamide/biurea is rapid, occurring predominantly via the urine, and there is very little systemic retention of biurea.

Azodicarbonamide is of low acute toxicity and does not cause skin, eye, or respiratory tract irritation in experimental animals. Results from a poorly conducted skin sensitization study were negative, and there was no evidence of an asthmatic-type response in guinea-pigs in one study. No adverse effects were observed in experimental animals inhaling up to 200 mg/m^3 for up to 13 weeks. Repeated oral exposures resulted in the appearance of pyelonephritis with casts and crystalline deposits in renal tubuli in several species. However, the dose levels required to induce these effects were high (>200 mg/kg body weight per day in studies of up to 1 year's duration). Although azodicarbonamide was found to be a mutagen in bacterial systems, there is no evidence that this effect would be expressed *in vivo*. The carcinogenicity and reproductive toxicity of azodicarbonamide have not been examined in detail, but no tumorigenic or antifertility effects were observed in early studies in which animals were treated with the breakdown product biurea. Developmental toxicity has not been studied.

Studies in humans have concentrated solely on the ability of azodicarbonamide to induce asthma and skin sensitization. Evidence that azodicarbonamide can induce asthma in humans has been found from bronchial challenge studies with symptomatic individuals and from health evaluations of employees at workplaces where azodicarbonamide is manufactured or used. There are also indications that azodicarbonamide may induce skin sensitization.

On the basis that azodicarbonamide is a human asthmagen and that the concentrations required to induce asthma in a non-sensitive individual or to provoke a response in a sensitive individual are unknown, it is concluded that there is a risk to human health under present occupational exposure conditions. The level of risk is uncertain; hence, exposure levels should be reduced as much as possible.

Data have been identified that indicate ethyl carbamate formation in consumer products such as bread and beer following the addition of azodicarbonamide. Exposure of the general public to azodicarbonamide could not be evaluated because of the lack of available data.

Azodicarbonamide released to surface waters would partition to the hydrosphere with no significant sorption to particulates. The half-life for reaction with hydroxyl radicals in the atmosphere is calculated to be 0.4 days. Azodicarbonamide was readily biodegradable in two out of three tests with sewage sludge and was degraded in soil by 20–70% over 14 days. No-observed-effect concentrations (NOECs) for fish and the water flea have been reported at $50 and 5 mg/litre, respectively. Lack of information on release to the environment precludes a quantitative risk assessment.

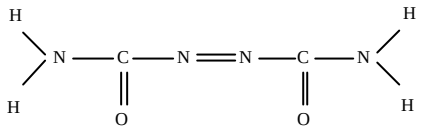
2. IDENTITY AND PHYSICAL/CHEMICAL PROPERTIES

Azodicarbonamide (CAS No. 123-77-3) is a synthetic chemical that exists at ambient temperature as a yellow-orange crystalline solid. It is poorly soluble in water at 20 °C (<50 mg/litre), although it is slightly soluble in hot water. It is insoluble in many organic solvents, but it is soluble in *N*,*N*-dimethyl formamide and dimethyl sulfoxide. It has a very

low vapour pressure (2.53×10^{-11} kPa at 20 °C). Additional physical/chemical properties are presented in the International Chemical Safety Card reproduced in this document.

Common synonyms for azodicarbonamide are ADA, ADC, azobiscarbonamide, azobiscarboxamide, azodicarbodiamide, azodicarboxamide, azodiformamide, azobisformamide, 1,1'-azobisformamide, diazene-dicarboxamide, and diazenedicarbonic acid amide. Trade names are listed in the International Chemical Safety Card appended to this document.

Azodicarbonamide's structural formula is shown below:



The conversion factors for azodicarbonamide at 20 °C and 101.3 kPa are as follows:

1 mg/m^3 = 0.21 ppm
1 ppm = 4.8 mg/m^3

3. ANALYTICAL METHODS

Two methods can be used to measure levels of azodicarbonamide in workplace air. In the first, samples are collected on 37-mm Teflon filters backed with polyethylene, which in turn is backed with a cellulose pad (Ahrenholz & Neumeister, 1987). Sampling takes place at 2 litres/min for periods from 7 to 486 min. After sampling, azodicarbonamide is recovered from the filter with dimethyl sulfoxide and analysed by high-performance liquid chromatography. The limit of quantification is given as 5 μg per sample. For a 15-min sample at 2 litres/min, this is equivalent to a quantification limit in air of 0.167 mg/m^3; over 8 h, it is equivalent to 0.005 mg/m^3.

In the second method, azodicarbonamide is collected on 37-mm glass fibre filters at 15–20 litres/min (Vainiotalo & Pfaffli, 1988). It is then eluted from the filter with dimethyl sulfoxide. Following the addition of sodium hydroxide and glucose solutions, the azodicarbonamide is reduced to hydrazine. This is reacted with 4-dimethylaminobenzaldehyde, and the resulting aldazine is measured spectrophotometrically at 460 nm. The lower detection limit is given as 0.001 mg/m^3 for a 4-m^3 air sample (equivalent to 4 μg per sample). This is a considerably larger volume than would normally be collected for assessing personal exposure samples. At a more typical flow rate of 2 litres/min for 8 h, 960 litres of air would be sampled, resulting in a detection limit of about 0.005 mg/m^3. Sampling over 15 min at the same rate would give a detection limit of about 0.16 mg/m^3.

Although there are published methods for measuring azodicarbonamide and its metabolite biurea in rats (Bechtold et al., 1989; see also Mewhinney et al., 1987), there are no reports describing their measurement in human body fluids.

4. SOURCES OF HUMAN AND ENVIRONMENTAL EXPOSURE

The principal end use of azodicarbonamide is as a blowing agent in the rubber and plastics industries. It is used in the expansion of a wide range of polymers, including polyvinyl chloride, polyolefins, and natural and synthetic rubbers. The blowing action occurs when the azodicarbonamide decomposes on heating (process temperatures ~190–230 °C) to yield gases (nitrogen, carbon monoxide, carbon dioxide, and ammonia), solid residues, and sublimated substances. Decomposition accelerators, in the form of metal salts and oxides, may also be added to bring about decomposition at lower temperatures.

Azodicarbonamide has in the past been used in the United Kingdom and Eire (but not other European Union member states) as a flour improver in the bread-making industry, but this use is no longer permitted. It is not known how common this practice is worldwide. Azodicarbonamide is not used in other consumer products.

Azodicarbonamide is manufactured by the reaction of dihydrazine sulfate and urea under high temperature and pressure. The product of this reaction is then oxidized using sodium chlorate and centrifuged to yield a slurry containing azodicarbonamide. The slurry is washed to remove impurities and dried to obtain the azodicarbonamide powder. This is then micronized to a fine powder (95% of particles <10 μm, which is in the respirable range for humans) before packaging.

Very limited information is available on production volumes. The Hazardous Substances Data Bank (HSDB, 1996) gives US production figures of "greater than 4.54 tonnes." Until recently, azodicarbonamide was produced in the United Kingdom; however, this production has now stopped, and all azodicarbonamide used in the United Kingdom is imported, predominantly through one large company. Approximately 2500 tonnes are supplied to the United Kingdom market each

year. Both pure azodicarbonamide (approximately 2200 tonnes) and pre-mixed formulations (300 tonnes) are supplied, the latter containing between 10 and 95% azodicarbonamide, depending on the end use application. "Masterbatch" products, in which the azodicarbonamide is pelletized with polyolefins, and blended pastes (azodicarbonamide and plasticizer) are also supplied to the rubber and plastics industries. In addition to the main importer, there are some firms that process azodicarbonamide into dust-suppressed powders, pastes, and "Masterbatch" formulations before selling the processed azodicarbonamide to the end users.

Recent studies have examined the contribution of azodicarbonamide to the levels of ethyl carbamate in bread and beer (Canas et al., 1997; Dennis et al., 1997a,b). It is not clear if unreacted azodicarbonamide is present in these products; therefore, it is not possible to assess the contribution that consumption of such products might make to the overall body burden of azodicarbonamide.

5. ENVIRONMENTAL TRANSPORT, DISTRIBUTION, AND TRANSFORMATION

A calculated half-life of 0.4 days for reaction with hydroxyl radicals in air has been reported.[1]

Azodicarbonamide added to five different soil types at 200 mg nitrogen/kg soil (dry weight) was degraded (measured as recovery of inorganic nitrogen) by between 21.1% and 66.1% over 14 days (Frankenberger & Tabatabai, 1982).

Degradation of azodicarbonamide by sewage sludge organisms has been investigated in three modified Sturm tests (Organisation for Economic Co-operation and Development [OECD] Guideline 301B). The compound was "readily biodegradable" in two out of the three tests and was degraded by 21% over 30 days in the third test (Uniroyal, 1992).[2]

According to Mackay Level I fugacity modelling, azodicarbonamide released to surface waters will partition to the hydrosphere with no significant sorption to particulates.[3]

6. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

6.1 Environmental levels

There are no data available on levels of azodicarbonamide in ambient air, water, soils, or sediment.

6.2 Human exposure

The data available to the authors of this CICAD are restricted to the occupational environment. It is estimated that several thousand persons are exposed to azodicarbonamide in the workplace in the United Kingdom. Of this total, it is estimated that only a few hundred persons are exposed as part of their main work activity (i.e., those involved in compounding, mixing, or raw material handling).

Data obtained by the United Kingdom's Health and Safety Executive at a plant milling azodicarbonamide powder in micronizing mills (four samples were collected in total) showed average personal exposures during the day shift to be 11.8 and 9.8 mg/m^3 and during the night shift to be 2.3 and 2.8 mg/m^3 because of the lower throughput at night. Samples were collected over 4 h. The operators' tasks involved bagging, weighing, and packaging the milled product.

In the published literature, Slovak (1981) reported time-weighted average total dust levels in the range 2–5 mg/m^3 for azodicarbonamide manufacturing operations. However, no details were given concerning occupational groups or tasks. A US National Institute for Occupational Safety and Health study (Ahrenholz et al., 1985) examined personal exposures of workers handling azodicarbonamide in a flooring factory. The work involved the formulation of pastes or paints and required the blending of azodicarbonamide powder with plasticizers, resins, pigments, and other additives. Exposures to azodicarbonamide occurred primarily while the workers were weighing and tipping the powder. Short-term (sample duration <70 min) personal exposures were in the range 0.15–12 mg/m^3 (median 2.7 mg/m^3). A second study (Ahrenholz & Anderson, 1985) focused on the use of azodicarbonamide in the injection moulding of plastics. The process involved blending azodicarbonamide powder with resins. Two sets of full-shift

[1] Bayer, unpublished calculated value (1988) based on the method of Atkinson; value presented in IUCLID (European Union database), version dated 7 February 1996.

[2] Bayer, unpublished value (1991) presented in IUCLID (European Union database), version dated 7 February 1996; no details available.

[3] Bayer remark in IUCLID (European Union database), version dated 7 February 1996.

measurements were reported, with median 8-h time-weighted average levels of 6.2 μg/m^3 (range, not detectable to 280 μg/m^3) and 25 μg/m^3 (range, trace to 752 μg/m^3), respectively.

No data are available relating to dermal exposure levels.

7. COMPARATIVE KINETICS AND METABOLISM IN LABORATORY ANIMALS AND HUMANS

No information is available on the toxicokinetics of azodicarbonamide in humans.

Most of the toxicokinetic data available for azodicarbonamide come from animal studies (Mewhinney et al., 1987). Absorption of azodicarbonamide has been demonstrated following both a single inhalation exposure of up to 6 h (34% of dose) and a single oral administration (10–33% of dose) of radiolabelled azodicarbonamide to rats. In contrast, approximately 90% of a single intratracheally instilled dose was apparently absorbed. The difference in absorption between inhaled and intratracheally instilled azodicarbonamide could be related to the fact that much of the inhaled azodicarbonamide did not reach the lower respiratory tract. Half an hour after a 6-h nose-only exposure of rats to 25 mg/m^3 of a dry aerosol (average mass aerodynamic diameter 3.4 μm), 78% of the calculated total intake was located in the gastrointestinal tract.

Following exposure by both inhalation and oral routes, substantial quantities of the substance remain unabsorbed from the gastrointestinal tract and are passed out in the faeces. Azodicarbonamide is readily converted to biurea, the only breakdown product identified, and it is likely that systemic exposure is principally to this derivative rather than to the parent compound. Elimination of absorbed azodicarbonamide/biurea is rapid, occurring predominantly via the urine, and there is very little systemic retention of biurea.

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

It is noted that some of the available toxicological studies were conducted using biurea. Azodicarbonamide readily undergoes reduction in the presence of thiol groups to form the stable compound biurea. Given that thiol groups are also present in many biological molecules, there is the potential for this reaction to take place wherever azodicarbonamide encounters thiol groups in biological systems. This has been demonstrated in an experiment in which radiolabelled azodicarbonamide was added to fresh rat blood (Mewhinney et al., 1987). All radioactivity was in the form of biurea within 5 min when untreated blood was used. Radioactivity associated with azodicarbonamide was detected only in blood to which 5 mg unlabelled azodicarbonamide/ml blood was added. This level is very much greater than the levels that humans are likely to encounter.

8.1 Single exposure

Azodicarbonamide is of low acute toxicity by all relevant routes of exposure. The LC_{50} was greater than 6100 mg/m^3 in rats and mice exposed to a dry aerosol (median mass aerodynamic diameter 5.8 ± 2.25 μm [geometric standard deviation]) of azodicarbonamide for 4 h (IRDC, 1982a,b). No mortality was observed in rats given oral doses of up to 5000 mg/kg body weight (Loeser, 1976). The dermal LD_{50} was >2000 mg/kg body weight in rabbits following application of this substance under an occlusive dressing for 24 h (MB Research Laboratories Inc., 1986). Few specific toxic effects were observed in any single exposure study.

8.2 Irritation and sensitization

Although most studies were of uncertain quality and in many cases would not comply with modern regulatory standards, results of several skin and eye irritation studies indicate that azodicarbonamide should not be regarded as a skin or eye irritant (Kimmerle, 1965; Conning, 1966; Mihail, 1977; MB Research Laboratories Inc., 1986). In a study of respiratory irritation, in which guinea-pigs were exposed head only to azodicarbonamide in plethysmography tubes, either no changes or effects of doubtful significance were reported for various lung function parameters, indicating that irritation was minimal at concentrations up to 97 mg/m^3 for 1 h (Shopp et al., 1987).

Owing to the poor quality of the only available skin sensitization study (the concentration used for induction and challenge — a 1% solution in dimethyl formamide — was very low; only four guinea-pigs were used in the test group; and test sites were not occluded), it was not possible to draw any conclusions regarding the ability of azodicarbonamide to induce skin sensitization in animals (Stevens, 1967). No evidence of pulmonary irritation or asthmatic-type reactions (no changes in specific airways conductance, no evidence of histopathological effects on the upper or lower respiratory tract, and no evidence of circulating antibodies) was obtained in one study in which groups of 10 guinea-pigs were repeatedly exposed by inhalation to unconjugated azodicarbonamide at 0, 51, or 200 mg/m^3 for 6 h/day, 5 days/week, for 4 weeks (Gerlach et al., 1989).

8.3 Short-term exposure

Azodicarbonamide is of relatively low toxicity to animals repeatedly exposed by the inhalation or oral routes. In well-conducted 2-week inhalation studies, groups of 10 male and 10 female F344/N rats or B6C3F$_1$ mice were exposed to dry aerosols (median mass aerodynamic diameter 2 ：m) at 0, 2, 10, 50, 100, or 200 mg/m^3 for 6 h/day, 5 days/week (Medinsky et al., 1990). Investigations included analyses of methaemoglobin and blood cholinesterase and extensive macroscopic and microscopic pathology; no changes of toxicological significance were seen.

Groups of five male and five female mice received 0, 625, 1250, 5000, or 10 000 mg azodicarbonamide/kg body weight per day by oral gavage in corn oil, 5 days/week for 2 weeks.[1] Mortalities were observed at 1250 mg/kg body weight per day and above (presumably treatment related). Histopathologically, at 1250 mg/kg body weight per day and above, pyelonephritis with casts was seen in renal tubuli, and crystalline deposits were observed in renal tubuli and the urinary bladder.

A similar study was conducted in rats; again, there was a dose-related increase in mortality at 1250 mg/kg body weight per day and above and a similar profile of renal lesions, although effects were seen at 1250 mg/kg body weight per day and above in males and at 2500 mg/kg body weight per day and above in females.[1]

In one early and very briefly reported study, signs of toxicity, the nature of which was not reported, were seen in male rats given 300 mg azodicarbonamide/kg body weight per day for 5 days but not in rats given 200 mg/kg body weight per day (Kimmerle, 1965).

In another study designed to look for adverse effects in the thyroid (but only investigating the uptake of iodine in the thyroid gland and serum protein-bound iodine), no clear evidence of thyroid toxicity was found in rats given low-iodine diets containing 1, 5, or 10% azodicarbonamide or 5 or 10% biurea for periods ranging between 1 and 4 weeks (Gafford et al., 1971).

There are no data relating to the effects of repeated dermal exposures.

8.4 Long-term exposure

8.4.1 Subchronic exposure

Groups of 10 male and 10 female F344/N rats or B6C3F$_1$ mice were exposed to dry aerosols (median mass aerodynamic diameter 2 ：m) at 0, 50, 100, or 200 mg/m^3 for 6 h/day, 5 days/week, for 13 weeks (Medinsky et al., 1990). Investigations included analyses of various enzyme activities in urine, haematology, blood cholinesterase, serum triiodothyronine and thyroxine, vaginal cytology, sperm morphology, levels of azodicarbonamide and biurea in lungs and kidneys (Mewhinney et al., 1987), and extensive macroscopic and microscopic pathology; no changes of toxicological significance were seen.

Groups of 10 male mice received 1, 78, 156, 312, 625, or 1250 mg azodicarbonamide/kg body weight per day and groups of 10 female mice received 0, 156, 312, 625, 1250, or 2500 mg azodicarbonamide/kg body weight per day by oral gavage in corn oil, 5 days/week for 13 weeks.[1] In contrast to the 2-week study (see section 8.3), there were no mortalities and no histopathological abnormalities.

Groups of 10 male rats received 1, 100, 500, or 2500 mg azodicarbonamide/kg body weight per day and groups of 10 female mice received 0, 200, 1000, or 5000 mg azodicarbonamide/kg body weight per day by oral gavage in corn oil, 5 days/week for 13 weeks.[1] Mortality was observed only at 2500 mg/kg body weight per day in males and at 5000 mg/kg body weight per day in females. Histopathologically, pyelonephritis and crystalline deposits were observed in males at 2500 mg/kg body weight per day and in females at 5000 mg/kg body weight per day only.

8.4.2 Chronic exposure and carcinogenicity

The effects of long-term exposure to azodicarbonamide have not been well studied, and no conventional carcinogenicity studies are available. The only data come from l- and 2-year studies in which rats and dogs received diets containing various amounts of biurea. In the 1-year study, rats and dogs ate diets containing 5 or 10% biurea (Oser et al., 1965). One high-dose rat died, and body weight gain was slightly depressed in high-dose males. No other signs of toxicity were observed in rats at necropsy. Most dogs from both dose groups died. Necropsy revealed massive, multiple renal calculi, bladder calculi, and chronic pyelonephritis. However, the dogs that were selected for this study were of uncertain and variable origin; hence, no useful results could be obtained from them. The main constituent (comprising 80–100%) of the calculi was identified as biurea.

In the 2-year study, rats and dogs ate diets containing either bread baked with untreated flour but supplemented with 750, 2370, or 7500 mg biurea/kg or bread baked with flour containing 100 mg azodicarbonamide/kg (Oser et al., 1965). Controls received diets containing bread baked with untreated flour. Given that azodicarbonamide is readily converted to biurea (Joiner et al., 1963), it is likely that the animals receiving the bread baked with azodicarbonamide-treated flour were actually exposed to biurea. As with the previous

[1] IRDC, unpublished data; cited in BG Chemie (1995).

investigations, the dogs that were selected for this study were of uncertain and variable origin; hence, no useful results could be obtained from them. For rats, no treatment-related deaths occurred, and no adverse effects were observed that were considered to be treatment related. Assuming food consumption of 20 g/day and a mean body weight of 350 g, the dietary inclusion levels correspond to approximately 45, 140, and 450 mg biurea/kg body weight per day.

8.5 Genotoxicity and related end-points

Azodicarbonamide is mutagenic *in vitro*, inducing base-pair mutations in bacteria with and without metabolic activation (Pharmakon Research International, 1984a; Mortelmans et al., 1986; Hachiya, 1987).[1] In contrast, several standard *in vitro* assays in mammalian cell systems have yielded negative results; gene mutation assays in Chinese hamster ovary cells, using the hypoxanthine guanine phosphoribosyl transferase locus, and in mouse lymphoma cells, using the thymidine kinase locus, have been conducted, along with an *in vitro* liver unscheduled DNA synthesis assay and a sister chromatid exchange assay in Chinese hamster ovary cells (Pharmakon Research International, 1984b,c).[1,2] A positive result was obtained in a chromosomal aberration assay in Chinese hamster ovary cells, but the result was not reproducible.[2] Negative results were obtained in a sex-linked recessive lethal assay in *Drosophila* (Yoon et al., 1985). Two *in vivo* bone marrow micronucleus assays in mice conducted by the intraperitoneal route (0 or 150 mg azodicarbonamide/kg body weight) were available, both giving negative results (Pharmakon Research International, 1984d; Hachiya, 1987).

8.6 Reproductive and developmental toxicity

The only study that has been conducted[3] is a three-generation study in which rats were given diets containing up to 7500 mg biurea/kg (equivalent to approximately 450 mg/kg body weight per day) (Oser & Oser, 1963; Oser et al., 1965). For each generation, rats were mated twice, and the first litter was sacrificed at weaning. From the second litter, 10 males and 10 females were chosen at random to form the parents for the next generation. The study finished with the weaning of the F_3 generation. For each generation, fertility index (percentage of matings resulting in pregnancy), gestation index (number of pregnancies resulting in live litters), viability index (numbers of pups surviving 4 or more days), and lactation index (numbers of pups alive at 4 days surviving to weaning) were determined. No reproductive effects were observed.

The only other information available is that no organ weight or histological changes were observed in the reproductive organs of rats and mice repeatedly exposed for 13 weeks to up to 200 mg azodicarbonamide/m^3 by inhalation (see section 8.4.1, Medinsky et al., 1990).

The developmental toxicity of azodicarbonamide has not been studied.

8.7 Immunological and neurological effects

No studies are available that specifically investigate these end-points, and there is no relevant information from toxicity studies in animals.

9. EFFECTS ON HUMANS

The effects of exposure to azodicarbonamide in humans have not been fully evaluated. There are no data detailing the effects of single exposures by any route. The most frequently reported effects of repeated exposure to azodicarbonamide are respiratory symptoms as well as, to a lesser extent, skin sensitization reactions. There are no reports relating to the potential for azodicarbonamide to produce other systemic adverse effects. The potential genotoxic, carcinogenic, and reproductive effects of azodicarbonamide in exposed humans have not been studied.

9.1 Case reports

A number of reports have been published of individual azodicarbonamide workers alleging asthma induced by exposure to azodicarbonamide. The strongest evidence comes from a study of two individuals (one atopic and one non-atopic) who worked at the same plastics factory for about 4 years (Malo et al., 1985; Pineau et al., 1985). Both were

[1] T. Cameron, unpublished Ames and mouse lymphoma test results (1990) from the short-term test program sponsored by the Division of Cancer Aetiology, National Cancer Institute (cited in Chemical Carcinogenesis Research Information System [CCRIS] database, US National Cancer Institute).

[2] NTP, unpublished data on chromosome aberration and sister chromatid exchange assays in Chinese hamster ovary cells for azodicarbonamide, submitted to the National Toxicology Program, National Institutes of Health, US Department of Health and Human Services, Research Triangle Park, NC.

[3] The authors of this CICAD have been informed that a reproductive toxicity screening test is being conducted according to OECD test method 421.

intermittently exposed (1–2 weeks' duration, 3–4 times per year) to azodicarbonamide at work. A few months after their first encounter with azodicarbonamide, both developed symptoms described as "eye/nose irritation" at work, followed a few hours later by nocturnal asthmatic symptoms. After a 1-month period free from exposure, both subjects underwent lung provocation studies. Baseline values for forced expiratory volume in 1 s (FEV_1), forced vital capacity (FVC), and the concentration of histamine required to produce a 20% drop in FEV_1 ($PC_{20}H$) were obtained by spirometry. Both subjects performed a control challenge using lactose and then a 50:50 mixture of lactose and azodicarbonamide for 15 s on the next day. On both days, lung function was monitored to follow the time course of any response. It was reported that the trial was not carried out blind.

No effects on lung function were observed following challenge with lactose alone. After the azodicarbonamide challenge, however, the atopic individual developed a late respiratory response starting 3 h after challenge and reaching a maximum 24% drop in FEV_1 6 h after challenge. A drop in $PC_{20}H$ was also reported, demonstrating increased airway hyperreactivity, and this parameter did not return to the baseline value until 6 weeks after challenge. The non-atopic individual showed a dual response to azodicarbonamide. Peak reductions in FEV_1 of greater than 20% were recorded 30 min and 5–6 h after exposure. No significant reduction in $PC_{20}H$ was reported for the second individual. A control atopic subject with underlying asthma who worked in the same industry but did not experience work-related respiratory effects was also tested. His baseline $PC_{20}H$ was similar to that of the atopic subject, but no change in lung function was observed following a 15-min exposure to azodicarbonamide under similar conditions (as this subject had less reactive airways, a much longer exposure duration was utilized). Owing to the insolubility of azodicarbonamide, skin prick tests were not performed.

Six other cases have been reported in the literature, but in each case the evidence that azodicarbonamide was the cause of the respiratory symptoms is less strong. In some cases, there had been previous exposure in industries associated with potential exposure to other asthmagenic substances; for others, the bronchial challenge test was either poorly conducted or not conducted at all (Valentino & Comai, 1985; Alt & Diller, 1988; Normand et al., 1989).

Three case reports on skin sensitization have been published. In the most recently reported investigation, a male textile worker exposed to azodicarbonamide in foam ear-plugs was patch tested to discover the cause of a recurrent dermatitis of the ear (Nava et al., 1983; Bonsall, 1984; Yates & Dixon, 1988). No response was elicited with a number of standard (International Contact Dermatitis Research Group standard series) allergens. However, the individual gave a strong positive reaction to the ear-plugs at 48 and 96 h and also to azodicarbonamide (a component of the ear-plugs) at a concentration of 1 and 5% in petrolatum but not at 0.1% in petrolatum. Ten control subjects patch tested with 1 and 5% azodicarbonamide in petrolatum did not respond, and the individual reported no further symptoms upon discarding the ear-plugs.

9.2 Epidemiological studies

Workplace health surveys have also been carried out where azodicarbonamide was either manufactured or used to investigate the presence of respiratory symptoms in azodicarbonamide workers.

A prevalence study of occupational asthma was carried out among a group of 151 workers at a factory manufacturing azodicarbonamide (Slovak, 1981). Diagnosis of asthma was made on the basis of an administered questionnaire and a detailed occupational history taken by the author. The population was divided into three groups: those classified as potentially sensitized, on the basis of questionnaire results; those with daily exposure but without symptoms; and those with no exposure to azodicarbonamide or any other known sensitizer. On one day, pre- and post-shift spirometry was performed, and FEV_1, FVC, and the FEV_1/FVC ratio were determined. Skin prick tests were also attempted using both common allergens to determine atopic status and azodicarbonamide at concentrations of 0.1, 1, and 5% in dimethyl sulfoxide. Concurrent personal sampling measurements were made to determine the levels of airborne azodicarbonamide to which individuals were exposed.

Personal sampling indicated that, at the time of the investigation, airborne concentrations of azodicarbonamide ranged between 2 and 5 mg/m^3, as 8-h time-weighted averages. From the questionnaires and occupational histories, 28 individuals (18.5%) were diagnosed as having asthma apparently related to azodicarbonamide exposure. Twelve further cases of occupational asthma were identified from company records of past employees. Skin prick tests with azodicarbonamide could not be adequately performed owing to the insolubility of the substance.

Of the 28 current workers classified as sensitized, over half developed symptoms within 3 months of first exposure and 21/28 (75%) within 1 year. Symptoms and signs included shortness of breath, chest tightness, wheezing, cough, rhinitis, conjunctivitis, and rash. Reactions were of an immediate type for 6/28 (21%) individuals, late onset for 16/28 (57%), and dual onset for 6/28 workers. Of those showing a dual response, all but one had initially shown a late onset pattern. A total of 13/28 (46%) workers reported worsening of symptoms with

continuing exposure to azodicarbonamide and a shortening of the time between returning to work and reappearance of symptoms. Eight out of 13 workers exposed to azodicarbonamide for more than 3 months after development of symptoms also developed sensitivity to previously well-tolerated irritants (e.g., sulfur dioxide and tobacco smoke), which persisted for over a month after removal from exposure to azodicarbonamide. In five individuals, this airway hyperreactivity persisted for over 3 years. There were no changes in FEV_1 or FVC over the work shift in any group. In view of the latency in development of effects, late or dual onset of symptoms in 12/28 (43%) symptomatic workers, increase in sensitivity with repeated exposure, and the persisting lung hyperreactivity in workers with prolonged exposure after developing symptoms, it seems likely that these individuals had become sensitized to azodicarbonamide.

Ahrenholz & Anderson (1985) and Whitehead et al. (1987) conducted detailed investigations of the workforce at a plastics factory employing about 325 workers. Lung function tests and interviews to gather information on occupational history, smoking habits, past illnesses, and respiratory, nasal, eye, and skin irritation, including the time course of any symptoms, were carried out with a large percentage of the workforce. There were no clear differences in the results of lung function studies between those exposed to azodicarbonamide and non-exposed individuals. However, responses to the questionnaire revealed a significant association between symptoms of irritation, cough, wheezing, shortness of breath, and headache and present or previous employment as an injection mould operator. There was also a slight but not statistically significant increase in the reporting of skin rash among those with current or previous work in the injection moulding department. The prevalence of all the above symptoms was reduced among those whose employment in this department was limited to the period before azodicarbonamide was introduced or after a change in the process significantly reduced the use of azodicarbonamide at the plant.

Personal sampling showed that concentrations of airborne azodicarbonamide ranged from below the limit of detection (0.001 mg/m^3) to 0.32 mg/m^3 (median 0.006 mg/m^3; geometric mean 0.004 mg/m^3) averaged over the full shift. The highest concentration of azodicarbonamide recorded (for an injection mould operator) was 0.01 mg/m^3. Toluene, styrene, phenols, and triphenyl phosphate were also detected at concentrations at or below the odour threshold for each substance.

Other personal sampling data for a group of 17 individuals revealed levels of azodicarbonamide ranging from traces to 0.8 mg/m^3 (median 0.03 mg/m^3; geometric mean 0.02 mg/m^3) averaged over the full shift. The second highest value recorded was 0.4 mg/m^3, and the next highest, 0.06 mg/m^3. A moderate although statistically significant reduction in FEV_1 (mean reduction of 64 ml) and FVC (mean reduction of 77 ml) occurred following shifts in which workers were exposed to azodicarbonamide. Coughing at work, wheeze, and chest tightness were also reported, and symptoms were apparently worse during the week than on Sunday.

A detailed investigation of the workforce at a plant making floor coverings was conducted after nosebleeds, mucous membrane irritation, and skin rashes were reported in workers handling azodicarbonamide (Ahrenholz et al., 1985). Two surveys were carried out. The initial survey revealed, in decreasing order of prevalence, symptoms of eye irritation, nose irritation, cough, nocturnal cough, shortness of breath, wheeze, and chest tightness. The more extensive follow-up survey was conducted 6 weeks later. Pre- and post-shift auscultation, lung function tests, and respiratory symptoms (recorded by questionnaire) were recorded. Blood samples were also taken for immunological investigations.

Responses to the questionnaire revealed 15/30 regularly exposed workers experiencing occupationally related lower respiratory tract symptoms (cough, wheeze, and shortness of breath) compared with 1/16 never-exposed workers. No significant differences in pre- and post-shift FEV_1 and FVC measurements were found. For those workers apparently not exposed to azodicarbonamide or exposed indirectly (working in the vicinity but not directly handling azodicarbonamide), levels (8-h time-weighted average) ranged from <0.001 to 0.1 mg/m^3. However, during weighing and charging operations, peaks of between 0.15 and 12 mg/m^3 (median 2.7 mg/m^3) were measured for individuals directly involved.

10. EFFECTS ON OTHER ORGANISMS IN THE LABORATORY AND FIELD

Azodicarbonamide has been tested under OECD Guideline protocols in one species of fish and in the water flea (*Daphnia magna*); results are in an unpublished industry report, which has not been peer-reviewed (see Table 1). A second study, not conducted to a protocol or under Good Laboratory Practices, showed no effect of an azodicarbonamide solution analysed at 8 mg/litre on the zebra fish (*Brachydanio rerio*).[1] There was no effect on oxygen consumption of sewage sludge organisms exposed over 3 h to azodicarbonamide at

[1] IUCLID (European Union database), version dated 7 February 1996.

Table 1: Acute studies on toxicity to aquatic organisms.

Organism	Protocol	End-point	Concentration (mg/litre)	Reference
Fathead minnow (*Pimephales promelas*)	OECD 203	96-h NOEC	$50	Uniroyal (1992)
Water flea (*Daphnia magna*)	OECD 202	48-h NOEC	4.8 (measured) ~16 (nominal)	Uniroyal (1992)
		48-h EC_{50} immobilization	11 (measured) 29 (nominal)	

>10 000 mg/litre (this is substantially greater than the solubility of the compound, and no information is available on how this concentration was achieved).[1] Overall, it is not possible to draw firm conclusions from these studies.

11. EFFECTS EVALUATION

11.1 Evaluation of health effects

11.1.1 Hazard identification and dose–response assessment

Some of the available toxicological studies have been conducted using biurea rather than azodicarbonamide. However, azodicarbonamide is readily converted to biurea *in vivo*. Hence, similar toxicological properties would be expected.

Azodicarbonamide is of low acute toxicity by all routes, and, although the animal studies are of uncertain quality, solid azodicarbonamide would not be regarded as a skin or eye irritant. With respect to respiratory tract irritation, no changes of toxicological significance were seen in guinea-pigs exposed to azodicarbonamide aerosol at concentrations up to 97 mg/m^3 for 1 h.

No conclusions could be drawn regarding skin sensitization potential from the available, poor-quality animal studies. Although there are currently no validated animal studies investigating asthmagenic potential, there was no evidence of pulmonary irritation or asthmatic-type reactions in guinea-pigs exposed to up to 200 mg azodicarbonamide aerosol/m^3 for 6 h/day, 5 days/week, for 4 weeks.

Similarly, there were no changes of toxicological significance seen among rats or mice exposed by inhalation to up to 200 mg azodicarbonamide aerosol/m^3 for 6 h/day, 5 days/week, for up to 13 weeks.

For repeated-dose studies using the oral route, data were inconsistent. In 2-year studies in which rats received up to 450 mg biurea/kg body weight per day, there were no adverse effects seen. Unpublished information suggests that no adverse effects were seen in male mice exposed to up to 1250 mg azodicarbonamide/kg body weight per day and in female mice exposed to up to 2500 mg/kg body weight per day for 13 weeks. However, shorter-term studies (2 weeks, also unpublished) indicated histological lesions in the kidneys of rats and mice of both sexes at 1250 mg/kg body weight per day or more. A 13-week study in rats indicated kidney lesions in males at 2500 mg/kg body weight per day, with no adverse effects observed at the next lowest exposure level, 500 mg/kg body weight per day. For female rats, kidney lesions were observed at 5000 mg/kg body weight per day, and no adverse effects were observed at 1000 mg/kg body weight per day. There were no data in relation to repeated dermal exposure.

Azodicarbonamide has been identified as a mutagen in bacterial systems, but it was not mutagenic in mammalian cell *in vitro* test systems or in two mammalian assays *in vivo* using bone marrow. It is therefore unlikely that the mutagenic properties displayed by azodicarbonamide in bacterial systems will be expressed *in vivo*. However, it is considered that a confirmatory *in vivo* study in a second tissue is desirable.

There are no adequate data available relating to carcinogenic, reproductive, or developmental effects; hence, it is not possible to evaluate the risk to human health for these end-points.

Several bronchial challenge studies have been reported, but only one provides reasonable evidence that the work-related asthmatic symptoms were due specifically to azodicarbonamide. This report is considered to show an asthmatic response and not an irritant response to azodicarbonamide on challenge. Animal studies suggest that airborne concentrations of up to 200 mg/m^3 can be tolerated with little or no pulmonary irritation, and it is unlikely that the levels used in the bronchial challenge tests approached those used in

[1] Bayer, unpublished value (1988) presented in IUCLID (European Union database), version dated 7 February 1996; no details available.

animal studies. The delay in response to azodicarbonamide challenge, the magnitude of reduction in FEV_1 accompanied by an increase in airway hyperreactivity in one individual, and the fact that a control individual with mildly hyperreactive airways did not respond to a much more prolonged exposure under similar challenge conditions provide further evidence for asthmagenicity. Further evidence of a link between azodicarbonamide and respiratory problems is provided by the results of workplace health evaluations. Although criticisms can be levelled at individual studies, weight of evidence suggests that azodicarbonamide can induce asthma in a significant proportion of exposed people.

There are some case reports of individuals with skin reactions to topically applied azodicarbonamide. For some of these, results are questionable. However, in workplace health surveys, the incidence of skin rash was found to be greater among workers regularly exposed to azodicarbonamide. Although no firm conclusions could be drawn from the poorly reported animal study, clear evidence of skin sensitization to azodicarbonamide in one individual and supporting evidence of skin problems from workplace health surveys lead to the conclusion that azodicarbonamide should be considered as a human skin sensitizer.

In conclusion, the key toxic effect of azodicarbonamide in humans is asthmagenicity. Evidence of this effect has been found from bronchial challenge studies and workplace health evaluations. From the information available, azodicarbonamide is considered to have a low potential for irritancy; thus, it is considered that the respiratory symptoms observed in these studies are most likely due to an asthmatic-type response rather than respiratory tract irritancy. There is no clear information on the levels that may have induced or provoked the state of asthma.

There is also information to indicate that azodicarbonamide can cause skin sensitization in humans.

11.1.2 Criteria for setting guidance values for azodicarbonamide

The main cause for concern relates to the risk of developing occupational asthma. There is no information available relating to dose–response relationships or levels associated with the induction of a hypersensitive state or provocation of an asthmatic response. Hence, it is not possible to reliably quantify the risk of developing occupational asthma.

11.1.3 Sample risk characterization

Using data obtained from a factory in the United Kingdom and published exposure data as an example (section 6.2), levels of airborne azodicarbonamide measured over periods of <70 min to 4 h of up to 12 mg/m^3 have been observed. Short-term peak exposures could be higher than this level.

In the United Kingdom occupational setting, it is recommended that a maximum exposure limit (MEL) be assigned to substances for which it has not been possible to identify a level of exposure that is without adverse effects on health. This is a non-health-based standard, and, in determining the most appropriate level for a MEL, consideration is taken of the level of control that it is reasonably practicable for industry to achieve. The MEL of 1 mg/m^3 (8-h time-weighted average) was based on a level of control that was deemed by tripartite agreement to be reasonably practicable under workplace conditions within the United Kingdom. There is also a continuing remit for industry to keep on reducing exposure levels as advances in technology make this possible. For substances that are asthmagens, it is also advisable to have a short-term exposure limit (STEL) to restrict peak exposures, as they may have a role in the induction and triggering of asthmatic phenomena. In the absence of any specific data that might advise adequately on the numerical value of the STEL, 3 mg/m^3 (15-min reference period) has been established.

As azodicarbonamide is a skin sensitizer, where skin contact can occur, there may be a risk of developing allergic dermatitis if suitable personal protective equipment is not used.

There is evidence to suggest that azodicarbonamide has been added to consumer products such as bread and beer. The limited toxicology database and lack of exposure data make it difficult to adequately assess the risk to humans potentially exposed; hence, there is a need for further information.

11.2 Evaluation of environmental effects

Lack of information on release to the environment precludes a quantitative risk assessment.

12. PREVIOUS EVALUATIONS BY INTERNATIONAL BODIES

Previous evaluations by international bodies were not identified. 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 preventive and protective measures and first aid recommendations, are presented in the International Chemical Safety Card (ICSC 0380) reproduced in this document.

13.1 Human health hazards

Azodicarbonamide is of low acute toxicity, but repeated or prolonged contact may cause asthma and skin sensitization.

13.2 Health surveillance advice

Physicians involved in worker health surveillance programmes should be aware of the potential of azodicarbonamide as a human asthmagen.

14. CURRENT REGULATIONS, GUIDELINES, AND STANDARDS

Information on national regulations, guidelines, and standards may be obtained from UNEP Chemicals (IRPTC), Geneva.

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.

AZODICARBONAMIDE

0380
October 1997

CAS No: 123-77-3
RTECS No: LQ1040000
UN No: 3242
EC No: 611-028-00-3

Diazenedicarboxamide
1,1'-Azobisformamide
$C_2H_4N_4O_2$ / $NH_2CON=NCONH_2$
Molecular mass: 116.1

TYPES OF HAZARD/ EXPOSURE	ACUTE HAZARDS/SYMPTOMS	PREVENTION	FIRST AID/FIRE FIGHTING
FIRE	Flammable. Gives off irritating or toxic fumes (or gases) in a fire.	NO open flames, NO sparks, and NO smoking.	Foam, powder.
EXPLOSION			
EXPOSURE		**PREVENT DISPERSION OF DUST! STRICT HYGIENE!**	
Inhalation	Cough. Headache. Shortness of breath. Sore throat. Wheezing. Fatigue. Cramps.	Local exhaust or breathing protection.	Fresh air, rest. Refer for medical attention.
Skin	Redness.	Protective clothing.	Remove contaminated clothes. Rinse and then wash skin with water and soap.
Eyes	Redness. Pain.	Safety goggles, or eye protection in combination with breathing protection.	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.	Rinse mouth. Give plenty of water to drink. Rest.

SPILLAGE DISPOSAL	PACKAGING & LABELLING
Sweep spilled substance into sealable containers; if appropriate, moisten first to prevent dusting. Carefully collect remainder, then remove to safe place (extra personal protection: P2 filter respirator for harmful particles).	Xn Symbol R: 42-44 S: (2-)22-24-37 UN Hazard Class: 4.1 UN Pack Group: II

EMERGENCY RESPONSE	STORAGE
Transport Emergency Card: TEC (R)-41G19	

IPCS
International Programme on Chemical Safety

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

SEE IMPORTANT INFORMATION ON THE BACK.

IMPORTANT DATA

Physical State; Appearance
ORANGE RED CRYSTALS OR YELLOW POWDER.

Chemical Dangers
The substance decomposes on heating or on burning producing toxic fumes (nitrogen oxides).

Occupational Exposure Limits
TLV not established.

Routes of Exposure
The substance can be absorbed into the body by inhalation of its aerosol.

Inhalation Risk
Evaporation at 20°C is negligible; a harmful concentration of airborne particles can, however, be reached quickly.

Effects of Short-term Exposure
The substance irritates the eyes and the respiratory tract. Inhalation of dust may cause asthmatic reactions (see Notes).

Effects of Long-term or Repeated Exposure
Repeated or prolonged contact with skin may cause dermatitis. Repeated or prolonged contact may cause skin sensitization. Repeated or prolonged inhalation exposure may cause asthma.

PHYSICAL PROPERTIES

Melting point (decomposes): 225°C 12117000
Relative density (water = 1): 1.65
Solubility in water: none

ENVIRONMENTAL DATA

NOTES

The symptoms of asthma often do not become manifest until a few hours have passed and they are aggravated by physical effort. Rest and medical observation are therefore essential. Anyone who has shown symptoms of asthma due to this substance should avoid all further contact with this substance. Genitron AC, Kempore 125, Porofor LK1074 and Unifoam AZ are trade names.

ADDITIONAL INFORMATION

REFERENCES

Ahrenholz S, Anderson K (1985) *Health hazard evaluation report of Leon Plastics, Grand Rapids, MI.* Cincinnati, OH, US Department of Health and Human Services (Report No. HETA-83-156-1622; PB89-143200).

Ahrenholz S, Neumeister C (1987) Development of a sampling and analytical method for azodicarbonamide. *American Industrial Hygiene Association journal*, 48(5):442–446.

Ahrenholz S, Morawetz J, Liss G (1985) *Health hazard evaluation report of Armstrong World Plastics, Lancaster, PA.* Cincinnati, OH, US Department of Health and Human Services (Report No. HETA-83-451-1547; PB86-105582).

Alt E, Diller W (1988) "Hyperreactivity cough" in occupational medicine. *Zentralblatt fuer Arbeitsmedizin, Arbeitsschutz und Prophylaxe Ergonomie*, 38 (Suppl. 2):22–26.

Ball E, Saleem A, Ogunbiyi A, Wiley K, Groves J (1996) *Azodicarbonamide; Criteria document for an occupational exposure limit.* Sudbury, Suffolk, Health and Safety Executive, HSE Books (ISBN 0 7176 10926).

Bechtold W, Medinsky M, Cheng Y, Hobbs C (1989) Azodicarbonamide: methods for the analysis in tissues of rats and inhalation disposition. *Xenobiotics*, 19:1003–1012.

BG Chemie (1995) Azodicarbonamide. In: GDCh-Advisory Committee on Existing Chemicals of Environmental Relevance, eds. *Toxicological evaluations, potential health hazards of existing chemicals. Vol. 8.* Stuttgart, S. Hirzel (ISBN 0 387 58287 8).

Bonsall J (1984) Allergic contact dermatitis to azodicarbonamide. *Contact dermatitis*, 10:42.

Canas B, Diachenko G, Nyman P (1997) Ethyl carbamate levels resulting from azodicarbonamide use in bread. *Food additives and contaminants*, 14(1):89–94.

Conning D (1966) *Azodicarbonamide (Genitron AC4). Toxicological report.* Unpublished report submitted to Imperial Chemical Industries Limited, Macclesfield (Report No. TR/522).

Dennis M, Massey R, Ginn R, Parker I, Crews C, Zimmerli B, Zoller O, Rhyn P, Osborne B (1997a) The effect of azodicarbonamide concentrations on ethyl carbamate concentrations in bread and toast. *Food additives and contaminants*, 14(1):95–100.

Dennis M, Massey R, Ginn R, Willetts P, Crews C, Parker I (1997b) The contribution of azodicarbonamide to ethyl carbamate formation in bread and beer. *Food additives and contaminants*, 14(1):101–108.

Frankenberger W, Tabatabai M (1982) Transformations of amide nitrogen in soils. *Soil Science Society of America journal*, 46:280–284.

Gafford F, Sharry P, Pittman J Jr (1971) Effect of azodicarbonamide (1,1-azobisformamide) on thyroid function. *Journal of clinical endocrinology and metabolism*, 32:659–662.

Gerlach R, Medinsky M, Hobbs C, Bice D, Bechtold W, Cheng Y, Gillett N, Birnbaum L, Mauderly J (1989) Effect of four week repeated inhalation exposure to unconjugated azodicarbonamide on specific and non-specific airway sensitivity of the guinea pig. *Journal of applied toxicology*, 9(3):145–153.

Hachiya N (1987) Evaluation of chemical genotoxicity by a series of short term tests. *Akita Igaku*, 14:269–292.

HSDB (1996) *Hazardous substances data bank*. Bethesda, MD, US National Library of Medicine. CHEM-BANK, SilverPlatter compact disk.

IPCS (1993) *International Chemical Safety Card — Diazenedicarboxamide.* Geneva, World Health Organization, International Programme on Chemical Safety (ICSC 0380).

IRDC (1982a) *Acute inhalation toxicity test with azodicarbonamide in rats.* Unpublished report submitted by the International Research and Development Corporation to the National Toxicology Program, National Institutes of Health, US Department of Health and Human Services, Research Triangle Park, NC (Report No. 5703-115).

IRDC (1982b) *Acute inhalation toxicity test with azodicarbonamide in mice*. Unpublished report submitted by the International Research and Development Corporation to the National Toxicology Program, National Institutes of Health, US Department of Health and Human Services, Research Triangle Park, NC (Report No. 5703-111).

Joiner R, Vidal F, Marks H (1963) A new powdered agent for flour maturing. *Cereal chemistry*, 40:539–553.

Kimmerle G (1965) *Toxicological studies on Porofor ADC, Urazol and plastic foam extracts.* Unpublished report, Institute of Toxicology, Bayer AG, Wuppertal-Elberfeld.

Loeser E (1976) *Acute oral toxicity: Porofor ADC/K.* Unpublished report, Institute of Toxicology, Bayer AG, Wuppertal-Elberfeld.

Malo J, Pineau L, Cartier A (1985) Occupational asthma due to azobisformamide. *Clinical allergy*, 15:261–264.

MB Research Laboratories Inc. (1986) *Acute dermal toxicity in rabbits. MB 86-83 93 B. Celogen AZ 120*. Unpublished report submitted to Uniroyal Chemical Company Inc., Middlebury, CN.

Medinsky M, Bechtold W, Birnbaurn L, Bond J, Burt D, Cheng Y, Gillett N, Gulati D, Hobbs C, Pickrell J (1990) Effect of inhaled azodicarbonamide on F344/N rats and B6C3F1 mice with 2-week and 13-week inhalation exposures. *Fundamental and applied toxicology*, 15:308–319.

Mewhinney J, Ayres P, Bechtold W, Dutcher J, Cheng Y, Bond J, Medinsky M, Henderson R, Birnbaum L (1987) The fate of inhaled azodicarbonamide in rats. *Fundamental and applied toxicology*, 8:372–381.

Mihail T (1977) *Studies of skin and mucous membrane tolerance: Porofor ADC/K*. Unpublished report, Institute of Toxicology, Bayer AG, Wuppertal-Elberfeld.

Mortelmans K, Haworth S, Lawlor T, Speck W, Trainer B, Zeiger E (1986) *Salmonella* mutagenicity tests: 11. Results from the testing of 270 chemicals. *Environmental mutagenesis*, 8 (Suppl. 7):1–119.

Nava C, Beretta F, Elena A, Ghizzi A, Pattarin R, Villa L (1983) Allergic dermatitis due to improvers and other flour additives. *Medicina del Lavoro*, 74(5):376–379.

Normand J, Grange F, Hernandez C, Ganay A, Davezies P, Bergeret A, Prost G (1989) Occupational asthma after exposure to azodicarbonamide: report of four cases. *British journal of industrial medicine*, 46:60–62.

Oser B, Oser M (1963) Nutritional studies on rats on diets containing high levels of partial ester emulsifiers. 11. Reproduction and lactation. *Journal of nutrition*, 60:489–505.

Oser B, Oser M, Morgareidge K, Stemberg S (1965) Studies of the safety of azodicarbonamide as a flour maturing agent. *Toxicology and applied pharmacology*, 7:445–472.

Pharmakon Research International (1984a) *Ames* Salmonella*/ microsome plate test (EPA/OECD). PH 301-UN-004-84. Celogen AZ-130.* Unpublished report submitted to Uniroyal Chemical Company Inc., Middlebury, CN.

Pharmakon Research International (1984b) *CHO/HGPRT mammalian cell forward gene mutation assay. PH 314-UN-003-84. Celogen AZ.* Unpublished report submitted to Uniroyal Chemical Company Inc., Middlebury, CN.

Pharmakon Research International (1984c) *Rat hepatocyte primary culture/DNA repair test. PH 311-UN-003-84. Celogen AZ-130.* Unpublished report submitted to Uniroyal Chemical Company Inc., Middlebury, CN.

Pharmakon Research International (1984d) *Micronucleus test (MNT) OECD. PH-309A-UN-003-84. Celogen AZ-130.* Unpublished report submitted to Uniroyal Chemical Company Inc., Middlebury, CN.

Pineau L, Cartier A, Malo J-L (1985) Occupational asthma due to azobisformamide. *Journal of allergy and clinical immunology*, 75:170.

Shopp G, Cheng Y, Gillet N, Bechtold W, Medinsky M, Hobbs C, Birnbaum L, Mauderly J (1987) Acute inhalation exposure of azodicarbonamide in the guinea pig. *American Industrial Hygiene Association journal*, 48(2):127–132.

Slovak A (1981) Occupational asthma caused by a plastics blowing agent, azodicarbonamide. *Thorax*, 36(12):906–909.

Stevens M (1967) Use of the albino guinea pig to detect the skin sensitising ability of chemicals. *British journal of industrial medicine*, 24:189–202.

Uniroyal (1992) Unpublished report from the Uniroyal Chemical Company Inc., Middlebury, CN.

Vainiotalo S, Pfaffli P (1988) Measurement of azodicarbonamide in workroom air in the plastics processing industry. *Annals of occupational hygiene*, 43:203–208.

Valentino M, Comai M (1985) Occupational asthma from azodicarbonamide: Case report. *Giornale Italiano di Medicina del Lavoro*, 7(2–3):97–99.

Whitehead L, Robins T, Fine L, Hansen D (1987) Respiratory symptoms associated with the use of azodicarbonamide foaming agent in a plastics injection moulding facility. *American journal of industrial medicine*, 11:83–92.

Yates V, Dixon J (1988) Contact dermatitis from azodicarbonamide in earplugs. *Contact dermatitis*, 19(2):155–156.

Yoon J, Mason J, Valencia R, Woodruff R, Zimmering S (1985) Chemical mutagenesis testing in *Drosophila*. IV. Results of 45 coded compounds tested for the National Toxicology Program. *Environmental mutagenesis*, 7:349–367.

APPENDIX 1 — SOURCE DOCUMENT

Ball et al. (1996): *Azodicarbonamide; Criteria document for an occupational exposure limit*

The authors' first draft was initially reviewed internally by a group of approximately 10 United Kingdom Health and Safety Executive experts (mainly toxicologists, but also scientists involved in other relevant disciplines, such as epidemiology and occupational hygiene). The toxicology section of the amended draft was then reviewed by toxicologists from the United Kingdom Department of Health. Subsequently, the entire criteria document was reviewed by a tripartite advisory committee to the United Kingdom Health and Safety Commission, the Working Group for the Assessment of Toxic Chemicals (WATCH). This committee is composed of experts in toxicology and occupational health and hygiene from industry, trade unions, and academia.

The members of the WATCH committee at the time of the peer review were Mr S.R. Bailey, Independent Consultant; Professor J. Bridges, University of Surrey; Dr H. Cross, Trade Unions Congress; Dr A Fletcher, Trade Unions Congress; Dr I.G. Guest, Chemical Industries Association; Dr A. Hay, Trade Unions Congress; Dr J. Leeser, Chemical Industries Association; Dr L. Levy, Institute of Occupational Hygiene, Birmingham; Mr A. Moses, Chemical Industries Association; Dr R. Owen, Trade Unions Congress; and Dr M. Sharratt, University of Surrey.

APPENDIX 2 — CICAD PEER REVIEW

The draft CICAD on azodicarbonamide 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

Health Canada, Ottawa, Canada

International Agency for Research on Cancer, Lyon, France

József Fodor National Center of Public Health, Budapest, Hungary

National Chemicals Inspectorate (KEMI), Solna, Sweden

National Institute of Public Health, Prague, Czech Republic

National Institute of Public Health and Environmental Protection, Bilthoven, The Netherlands

United States Department of Health and Human Services (National Institute for Occupational Safety and Health, Cincinnati, USA; National Institute of Environmental Health Sciences, Research Triangle Park, USA)

United States Environmental Protection Agency (Drinking Water Program, Denver, USA)

APPENDIX 3 — CICAD FINAL REVIEW BOARD

Tokyo, Japan, 30 June – 2 July 1998

Members

Dr R. Benson, Drinking Water Program, United States Environmental Protection Agency, Denver, CO, USA

Dr T. Berzins, National Chemicals Inspectorate (KEMI), Solna, Sweden

Mr R. Cary, Health Directorate, Health and Safety Executive, Merseyside, United Kingdom

Dr C. DeRosa, Agency for Toxic Substances and Disease Registry, Center for Disease Control and Prevention, Atlanta, GA, USA

Dr S. Dobson, Institute of Terrestrial Ecology, Cambridgeshire, United Kingdom

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

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

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

Ms M.E. Meek, Environmental Health Directorate, Health Canada, Ottawa, Ontario, Canada (*Chairperson*)

Dr J. Sekizawa, Division of Chem-Bio Informatics, National Institute of Health Sciences, Tokyo, Japan (*Vice-Chairperson*)

Professor S.A. Soliman, Department of Pesticide Chemistry, Alexandria University, Alexandria, Egypt

Ms D. Willcocks, Chemical Assessment Division, Worksafe Australia, Camperdown, Australia (*Rapporteur*)

Professor P. Yao, Chinese Academy of Preventive Medicine, Institute of Occupational Medicine, Beijing, People's Republic of China

Observers

Professor F.M.C. Carpanini,[1] Secretary-General, ECETOC (European Centre for Ecotoxicology and Toxicology of Chemicals), Brussels, Belgium

Dr M. Ema, Division of Biological Evaluation, National Institute of Health Sciences, Osakai, Japan

Mr R. Green,[1] International Federation of Chemical, Energy, Mine and General Workers' Unions, Brussels, Belgium

Dr B. Hansen,[1] European Chemicals Bureau, European Commission, Ispra, Italy

Mr T. Jacob,[1] Dupont, Washington, DC, USA

Dr H. Koeter, Organisation for Economic Co-operation and Development, Paris, France

Mr H. Kondo, Chemical Safety Policy Office, Ministry of International Trade and Industry, Tokyo, Japan

Ms J. Matsui, Chemical Safety Policy Office, Ministry of International Trade and Industry, Tokyo, Japan

Mr R. Montaigne,[1] European Chemical Industry Council (CEFIC), Brussels, Belgium

Dr A. Nishikawa, Division of Pathology, National Institute of Health Sciences, Tokyo, Japan

Dr H. Nishimura, Environmental Health Science Laboratory, National Institute of Health Sciences, Osaka, Japan

Ms C. Ohtake, Chem-Bio Informatics, National Institute of Health Sciences, Tokyo, Japan

Dr T. Suzuki, Division of Food, National Institute of Health Sciences, Tokyo, Japan

Dr K. Takeda, Mitsubishikasei Institute of Toxicological and Environmental Sciences, Yokohama, Japan

Dr K. Tasaka, Department of Chemistry, International Christian University, Tokyo, Japan

Dr H. Yamada, Environment Conservation Division, National Research Institute of Fisheries Science, Kanagawa, Japan

Dr M. Yamamoto, Chem-Bio Informatics, National Institute of Health Sciences, Tokyo, Japan

Dr M. Yasuno, School of Environmental Science, The University of Shiga Prefecture, Hikone, Japan

Dr K. Ziegler-Skylakakis, GSF-Forschungszentrum für Umwelt und Gesundheit GmbH, Institut für Toxikologie, Oberschleissheim, Germany

Secretariat

Ms L. Regis, International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland

Mr A. Strawson, Health and Safety Executive, London, United Kingdom

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

[1] Invited but unable to attend.

RÉSUMÉ D'ORIENTATION

Ce CICAD relatif à l'azodicarbonamide a été préparé à partir d'une étude du Health and Safety Executive du Royaume-Uni sur les risques pour la santé humaine (risques professionnels pour l'essentiel) (Ball et al., 1996). De ce fait, bien qu'il comporte un volet sur l'évaluation des données écologiques disponibles, il est principalement centré sur les risques pour la santé humaine sur les lieux de travail et tout particulièrement sur les voies d'exposition professionnelle à prendre en considération. L'analyse des données sur lesquelles repose l'étude a été arrêtée à juin 1994. Un dépouillement de la littérature a été ensuite effectué jusqu'à juillet 1997, à la recherche de données qui auraient pu être publiées depuis la fin de l'étude. Le document original ne prend pas en considérations les problèmes d'ordre écologique et comme le dépouillement de la littérature n'a pas permis de trouver trace de travaux qui leur soit consacrés, on n'a pas cherché à procéder à une évaluation des risques pour l'environnement. On trouvera à l'appendice 1 des indications sur les sources documentaires utilisées et sur leur mode de dépouillement. Les renseignements concernant l'examen du CICAD par des pairs font l'objet de l'appendice 2. Ce CICAD a été approuvé en tant qu'évaluation internationale lors d'une réunion du Comité d'évaluation finale qui s'est tenue à Tokyo (Japon) du 30 juin au 2 juillet 1998. La liste des participants à cette réunion figure à l'appendice 3. La fiche d'information internationale sur la sécurité chimique (ICSC No 0380) établie par le Programme international sur la Sécurité chimique (IPCS, 1993) est également reproduite dans ce document.

Les données toxicocinétiques sur l'azodicarbonamide (No CAS 123-77-3) sont limitées, mais ce composé se révèle être bien absorbé chez les rongeurs après inhalation ou ingestion. Une fraction notable de l'azocarbonamide traverse cependant les voies digestives sans être résorbé et se retrouve dans les matières fécales. L'azodicarbonamide est facilement transformé en biurée ou dicarbamylhydrazine, le seul métabolite qui ait été identifié et il est probable que l'exposition par la voie générale concerne ce dernier dérivé plutôt que la molécule initiale. Après absorption, l'élimination de l'azocarbonamide ou de la biurée est rapide et s'effectue principalement par la voie urinaire, la biurée étant très peu retenue dans l'organisme.

L'azocarbonamide présente une faible toxicité aiguë et il ne provoque pas d'irritation cutanée, oculaire ou respiratoire chez les animaux d'expérience. Des résultats négatifs ont été obtenu lors d'une étude de la sensibilisation cutanée, d'ailleurs mal conduite, et une autre étude, effectuée sur des cobayes, n'a pas révélé de réaction de nature asthmatiforme. Aucun effet indésirable n'a été observé chez des animaux de laboratoire à qui on en avait fait inhaler pendant des durées allant jusqu'à 13 semaines à des doses pouvant atteindre 200 mg/m^3. Une exposition répétée par la voie orale a entraîné des lésions évocatrices de pyélonéphrite avec présence intratubulaire de cylindres et de dépôts cristallins chez plusieurs espèces. Cependant, il a fallu une dose élevée pour provoquer ces effets (>200 mg/kg de poids corporel par jour sur une durée pouvant aller jusqu'à 1 an). L'azodicarbonamide s'est révélé mutagène sur des systèmes bactériens, mais il n'est pas certain que cet effet se produise *in vivo.* On n'a pas examiné en détail la cancérogénicité de l'azodicarbonamide, ni sa toxicité génésique, mais des études anciennes au cours desquelles des animaux avaient reçu son métabolite, la biurée, n'ont pas mis en évidence d'effets tumorigènes ou stérilisants. On n'a pas étudié son action toxique éventuelle sur le développement.

Les études relatives à la santé humaine portent uniquement sur l'aptitude de l'azodicarbonamide à provoquer de l'asthme ou une sensibilisation cutanée. Des épreuves d'exposition bronchique effectuées sur des sujets symptomatiques de même que l'examen médical de personnes employées à la fabrication d'azodicarbonamide ou sur des lieux ou on en utilisait, ont révélé que le composé pouvait provoquer de l'asthme chez l'Homme. Certains indices permettent également de penser qu'il peut provoquer une sensibilisation cutanée.

En se basant sur le fait que l'azodicarbonamide peut provoquer un asthme chez l'Homme et que l'on ignore à partir de quelle concentration cet asthme risque d'apparaître chez un sujet non sensible ou une réaction se manifester chez un sujet sensible, on est arrivé à la conclusion que dans les conditions actuelles d'exposition professionnelles, il y avait un risque pour la santé humaine. Compte tenu de l'incertitude sur la concentration à partir de laquelle il y a effectivement risque, il convient de réduire l'exposition le plus possible.

On possède des données indiquant qu'il se forme du carbamate d'éthyle dans certains produits de consommation comme le pain ou la bière après addition d'azodicarbonamide. Faute de données, il n'a pas été possible d'évaluer le degré d'exposition de la population générale à l'azodicarbonamide.

En cas de décharge dans les eaux superficielles, l'azocarbonamide se répartirait dans l'hydrosphère sans sorption importante aux matières particulaires. Dans le cas d'une réaction sur les radicaux hydroxyles de l'atmosphère, la demi-vie calculée est de 0,4 jour. Dans deux essais sur trois effectués avec des boues d'égout, on a constaté que l'azodicarbonamide se révélait facilement biodégradable et on observé une décomposition à 20-70 % dans le sol en 14 jours. La concentration sans effet observable pour les poissons et la puce d'eau a été trouvée respectivement égale à $50 et 5

mg/litre. En l'absence de renseignements sur la décharge d'azodicarbonamide dans l'environnement, on ne peut procéder à une évaluation quantitative du risque.

RESUMEN DE ORIENTACIÓN

Este CICAD sobre la azodicarbonamida se basa en un examen de los problemas relativos a la salud humana (fundamentalmente ocupacionales) preparado por la Dirección de Salud y Seguridad del Reino Unido (Ball et al., 1996). Por consiguiente, aunque el presente CICAD incluye una evaluación de los datos ecológicos disponibles, se concentra sobre todo en el riesgo para la salud humana en las condiciones del trabajo, con particular atención a la información acerca de las rutas que son de interés para el entorno ocupacional. En este examen se han incorporado los datos identificados hasta junio de 1994. Se realizó una ulterior búsqueda bibliográfica hasta julio de 1997 para localizar la información nueva que se hubiera publicado desde la terminación del examen. En el documento original no se abordaban los problemas relativos al medio ambiente; dado que en la búsqueda bibliográfica no se han encontrado estudios de interés de este sector, no se ha intentado realizar una evaluación del riesgo para el medio ambiente. La información acerca del carácter del examen colegiado del documento original y su disponibilidad figura en el apéndice 1. La información sobre el examen colegiado de este CICAD aparece en el apéndice 2. Este CICAD se aprobó como evaluación internacional en una reunión de la Junta de Evaluación Final celebrada en Tokio, Japón, del 30 de junio al 2 de julio de 1998. La lista de participantes en esta reunión figura en el apéndice 3. La Ficha internacional de seguridad química (ICSC 0380) para la azodicarbonamida, preparada por el Programa Internacional de Seguridad de las Sustancias Químicas (IPCS, 1993), también se reproduce en el presente documento.

Los datos toxicocinéticos sobre la azodicarbonamida (CAS Nº 123-77-3) son limitados, pero parece que se absorbe bien en roedores por inhalación y por vía oral. Quedan sin absorber cantidades importantes de la sustancia en el sistema gastrointestinal, que se eliminan en las heces. La azodicarbonamida se convierte fácilmente en biurea, único producto de la biodegradación identificado, y es probable que haya exposición sistémica fundamentalmente a este derivado y no al compuesto original. La eliminación de la azodicarbonamida/biurea absorbida es rápida, sobre todo a través de la orina, y hay una retención sistémica de biurea muy escasa.

La toxicidad aguda de la azodicarbonamida es baja y en los animales de experimentación no produce irritación cutánea, ocular o del aparato respiratorio. Los resultados de un estudio de sensibilización cutáneo poco fidedigno fueron negativos y en otro estudio no se obtuvieron pruebas de una respuesta de tipo asmático en cobayas. No se detectaron efectos adversos en animales de experimentación que inhalaron hasta 200 mg/m^3 durante 13 semanas. La exposición oral repetida provocó pielonefritis con cilindros y depósitos cristalinos en los túbulos renales en varias especies. Sin embargo, las dosis necesarias para inducir estos efectos fueron altas (>200 mg/kg de peso corporal al día en estudios de hasta un año de duración). Si bien se observó que la azodicarbonamida era mutagénica en sistemas bacterianos, no hay pruebas de que este efecto aparezca *in vivo.* No se han examinado con detalle la carcinogenicidad y la toxicidad reproductiva de la azodicarbonamida, pero en estudios iniciales en los cuales se trataron animales con el producto de degradación, la biurea, no se detectaron efectos tumorígenos o anticonceptivos. No se ha estudiado la toxicidad en el desarrollo.

Los estudios en el ser humano se han concentrado exclusivamente en la capacidad de la azodicarbonamida para inducir asma y sensibilización cutánea. En estudios de estímulo bronquial de personas sintomáticas y en evaluaciones de la salud de los empleados en lugares donde se fabrica o utiliza azodicarbonamida se ha comprobado que este producto puede inducir asma en el ser humano. Existen asimismo indicios de que la azodicarbonamida puede inducir sensibilización cutánea.

A partir de la base de que la azodicarbonamida es un asmógeno humano y de que no se conocen las concentraciones que se requieren para inducir el asma en una persona no sensible o provocar una respuesta en una persona sensible, se llega a la conclusión de que existe un riesgo para la salud humana en las condiciones actuales de exposición ocupacional. El nivel del riesgo es incierto; por consiguiente, se deben reducir al máximo los niveles de exposición.

Se conocen datos que indican que se forma etilcarbamato en productos de consumo como el pan y la cerveza después de la adición de azodicarbonamida. La exposición del público general no se pudo evaluar debido a la falta de datos disponibles.

La azodicarbonamida liberada en las aguas superficiales se distribuiría en la hidrosfera con una sorción no significativa en partículas. La semivida para la reacción en la atmósfera con los radicales hidroxilo se calcula que es de 0,4 días. La biodegradación de la azodicarbonamida fue fácil en dos de las tres pruebas realizadas con lodos cloacales y la degradación en el suelo fue del 20%-70% en un período de 14 días. No se han notificado concentraciones sin efectos observados (NOEC) para peces y pulgas de agua a $50 y 5 mg/litro, respectivamente. La falta de información sobre la liberación en el medio ambiente impide una evaluación cuantitativa del riesgo.