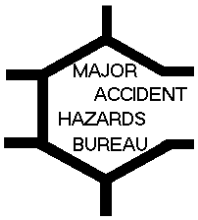
INSTITUTE FOR SYSTEMS INFORMATICS AND SAFETY



CARCINOGENS

IN THE CONTEXT OF COUNCIL DIRECTIVE 96/82/EC

REPORT BY TECHNICAL WORKING GROUP 8

Edited by

Michalis Christou

JOINT RESEARCH CENTRE

EUROPEAN COMMISSION

April 2000 **EUR 19650 EN**

Acknowledgements

This report has been developed by the Commission, DG ENV E.1 and JRC-MAHB, in close collaboration with the members of Technical Working Group 8 on Carcinogens, appointed for this purpose by DG ENV (see composition below). The valuable contributions of the members of the Working Group, not only in the preparation of this report, but throughout the work of TWG 8, are gratefully acknowledged.

Composition of Technical Working Group 8

Chairman: J. WETTIG, European Commission – DG ENV E.1 (until March 1999)

S. DUFFIELD, European Commission – JRC – MAHB (from March 1999)

Scientific Secretary: M. CHRISTOU, European Commission – JRC – MAHB

P. DILARA, European Commission – JRC – MAHB (until September 1997)

Members of the Group and invited experts (in alphabetical order):

A. AALTO, Ministry of Social Affairs and Health, *Finland*
R. BENIGNI, Istituto Superiore di Sanita', *Italy*
I. BROOKE, Health and Safety Executive, *United Kingdom*
L. DRAGSTED, Institute of Food Safety and Toxicology, *Denmark*
S. EBERHARTINGER, Ministry of Environment, Youth & Family, *Austria*
E. FASSOLD, European Commission - JRC, European Chemicals Bureau
H. FLEIG, BASF, CEFIC
J. HART, European Commission - JRC, European Chemicals Bureau
J. JARRY, Ministere de l'Environnement, *France*
P.B. LARSEN, Danish Environmental Protection Agency, *Denmark*
L. LOYON, Ministere de l'Environnement, *France*
D. Mc GREGOR, International Agency for Research on Cancer (IARC)
M. MELDRUM, Health and Safety Executive, *United Kingdom*
C. MERZ, SAIS, *Germany*
N. MITCHISON, European Commission - JRC, MAHB
C. NESSEL, CONCAWE
F. RUIZ BOADA, Ministerio de Interior, *Spain*
T. SANNER, Dept. Environmental & Occupational Cancer, *Norway*
T. SVENSSON, National Chemicals Inspectorate, *Sweden*
R. VAN LOO, Ministry of Housing, Spatial Planning and Environment, *Netherlands*

TABLE OF CONTENTS

1. INTRODUCTION

On 9 December 1996 *Directive 96/82/EC on the control of major-accident hazards* (so-called Seveso II Directive) was adopted by the Council of the European Union. Following its publication in the *Official Journal (OJ) of the European Communities (No L 10 of 14 January 1997)* the Directive entered into force on 3 February 1997.

The Seveso II Directive aims at the *prevention* of major-accident hazards involving dangerous substances and the *limitation of the consequences* of such accidents not only for man (*safety and health aspects*) but also for the environment (*environmental aspect*). Both aims should be followed with a view to ensuring high levels of protection throughout the Community in a consistent and effective manner.

Member States had up to two years to bring into force the national laws, regulations and administrative provisions to comply with the Directive (transposition period). From 3 February 1999, the obligations of the Directive have become mandatory for industry as well as the public authorities of the Member States responsible for the implementation and enforcement of the Directive. The Seveso II Directive has replaced the original Seveso Directive of 1982 (*Directive 82/501/EEC on the major-accident hazards of certain industrial activities; OJ No L 230 of 5 August 1982).*

The scope of the Seveso II Directive is defined by the presence, real or anticipated, of hazardous substances in quantities exceeding certain qualifying quantities (or threshold levels). Annex I of the Directive contains a list of named substances (Part 1) and a list consisting of *generic classification criteria* for substances and preparations such as toxic, explosive or flammable (Part 2).

The list of named substances in Annex I, Part 1 includes a list of 'carcinogens', to which is assigned a low qualifying quantity of 1 kg. Other named substances mentioned in Annex I, Part 1 also have carcinogenic properties, but they are not explicitly named as carcinogens in the Directive. All the carcinogens listed in Annex I, Part 1 were already included, with the same low qualifying quantity, in the list of named substances under the original Seveso Directive.

During discussions over the new Seveso II Directive in Council, questions were raised concerning the scientific and practical basis for the list of named carcinogens. It was stated that the intention was to cover a limited range of substances for which there was reason to suppose that they could have a carcinogenic effect after a single exposure, but there was agreement that the scientific basis for both the set of substances named and the threshold defined was limited and questionable. Eventually, the Council, when adopting the Seveso II Directive, requested the Commission to carry out a detailed examination of the list, in co-operation with the Member States, and to submit a report accompanied, if appropriate, by proposals for amending the list. The relevant statement in the Council Minutes reads as follows:

"The Council and the Commission acknowledge the need to evaluate the list of carcinogens in Part 1. The Council accordingly invites the Commission in conjunction with the Member States to examine in depth the substances to be retained and their appropriate qualifying quantities in the light of criteria such as their environmental persistence and the risks of exposure thereto, within the framework of the objectives of this Directive. Not later than two years after the entry into force of the Directive, the Commission will submit a report on the subject together, if appropriate, with a proposal for amending the list of carcinogens in Part 1."

As a result of this the Commission, after consulting with the Committee of Competent Authorities (CCA) set up under the original Seveso Directive, called a first meeting (12-13 June 1997) of a group of experts on carcinogenic substances with a view to working out how best to carry out this examination. As a result of the work carried out by the experts concerned before and at the meeting, and of further discussions in the CCA, it was subsequently decided to tackle the work task through this group, which was therefore constituted as a Technical Working Group (TWG 8).

The constitution of the group was primarily based on nominations from the Competent Authorities. Furthermore, internationally renowned experts that could contribute to the work of TWG 8 were invited to the meetings of the group. TWG 8 reported to the CCA.

Between June 1997 and December 1999, four meetings of TWG 8 were held in Ispra/Italy at the premises of the Major Accident Hazards Bureau (MAHB) established within the Joint Research Centre (JRC) of the European Commission. The MAHB was founded in February 1996 with a remit to offer scientific and technical support to other services of the Commission (principally DG Environment) in the successful implementation of European Union policy on the control of major industrial hazards and the prevention and mitigation of major accidents, in particular in connection with the Seveso Directives.

An interim report summarising the opinions of experts issued at the 3rd meeting of TWG 8 (24th-25th March 1999) and containing recommendations from this meeting was presented to the 1st meeting of the CCA established under the Seveso II Directive that was held on 19-21 May 1999 in Munich/Germany. In the light of the comments made by the CCA and taking into account the results of the 4th and last meeting of TWG 8 (14-15 December 1999), this Final Report was drawn up.

2. THE METHODOLOGY

2.1. Scientific Basis

The group discussed in some detail the scientific basis for deciding whether and to what extent substances present a danger of carcinogenesis in the event of a major accident. The following important points resulted from this discussion:

- The data on carcinogens are often sketchy, particularly for short exposure times.

- Carcinogens differ substantially in their potency - in other words the quantity of substance required to have a given carcinogenic effect. Animal experiments have shown differences of at least 9 orders of magnitude between the potencies of different carcinogens, and there is no reason to believe that these differences are not in some way reflected in potency on human beings. Clearly the potency is relevant when considering what qualifying quantity should be applied to a substance. It may also be of relevance when considering whether a substance should be covered at all as a carcinogen, especially for the many substances which are classified as *toxic* or *very toxic* and are also carcinogenic: if the danger of acute toxicity is much greater in the event of an accident than that of carcinogenesis, then the qualifying quantity for the Seveso II Directive should be based on acute toxicity.

- It is not certain whether substances with known carcinogenic properties can be "one-shot carcinogens". However, it seems reasonable not to exclude the possibility. There is some correlation between carcinogens for which a "one-shot" effect can be suspected and those which are of high potency. For many carcinogens, the persistence in the body is known; for some - but not all - the mechanism of carcinogenesis is believed to be known (e.g. endocrine-mediated; genotoxicity). Where these two questions can be answered, between them they can provide suggestive evidence for or against the "one-shot" hypothesis.

- Certain substances are agreed to be potent carcinogens. There is no current general agreement on how to assess potency. However, it became clear during our discussions that the corresponding EU working groups were considering proposals to use a particular tumorigenic dose descriptor, called "T25".

- Classification as a "category 1", "category 2", or "category 3" carcinogen is of limited value when considering single-shot exposure. This classification is based on the strength of evidence of carcinogenicity, and not on the potency.

- Considering these points, the group decided to pay particular attention to high-potency carcinogens, and to medium-potency carcinogens where there was evidence suggesting the possibility of "one-shot" effects. The group also studied those medium-potency carcinogens which are produced in large volumes in the EU.

2.2. Substances already named in Annex I Part 1

As instructed by the CCA, the group excluded from consideration all substances which were already named in Annex I Part 1 of the Directive (other than the list of named carcinogens), on the grounds that these substances had already been the subject of a decision based on all their properties, including carcinogenicity where appropriate.

The group also decided to include in the provisional list the substances already contained in the list of 'carcinogens'. This decision was based on the following considerations:

- All these substances have already been included in the original Seveso Directive, at the same qualifying quantity, since 1982.

- Some of these substances are now banned, or very little used.

- However, in no case has there been clear scientific evidence showing that the substance concerned is not carcinogenic, or is a very much less potent carcinogen than was initially believed.

- A decision to exclude these substances from the list of carcinogens could therefore only be based on considerations such as these substances not being used anymore. Since in many cases the reason why they are not in use anymore is that industry decided to avoid using them because of their unpleasant properties (including carcinogenesis), it was felt that excluding them now would send out a wrong signal that might even cause new developments leading to an increased use of these substances.

2.3. List examined

On the basis of the considerations outlined above, a large number of substances were screened by the technical working group. Of the 73 substances identified, the following list was drawn up for further examination:

- Acrylamide
- Diazomethane
- 1,2-Dibromo-3-chloropropane
- 1,2-Dimethylhydrazine
- Dimethyl sulphate
- Methylaziridine (Propyleneinine)

- 4-Methyl-m-phenylenediamine

- Diethyl sulphate
- Benzotrichloride
- Hydrazine
- Epichlorohydrin
- 4,4'-Diaminodiphenylmethane
- 1,2-Dibromoethane
- The list of substances already present in Annex I Part 1 as named carcinogens
- Compounds of the following metals: Beryllium, Cadmium, Chromium, Cobalt

2.4. Final list

Each substance in the list given above was then studied in detail. In each case the T25 data where available, physicochemical and biological properties, the mechanism of carcinogenicity, EU / IARC / other classification, evidence on the potential capability to act as a single exposure carcinogen, and information from the CCA were evaluated, and the group as a whole decided whether or not to include it in the final proposal. In the following section these discussions are summarised for each substance. The final list of substances proposed is presented in Chapter 5.

2.5. Qualifying quantities

Once the final list had been established, the group considered what qualifying quantities would be appropriate. Their proposal is presented in Chapter 6.

3. INDIVIDUAL INVESTIGATIONS ON NEW SUBSTANCES

3.1. ACRYLAMIDE (CAS No: 76-06-1; EC No: 201-173-7)

Current classification: Carc. Cat 2; R45, Mut. Cat 2; R46, T;R24/25-48/23/24/25
Acute toxicity: Toxic (rat female oral, LD50 = 490 mg/kg)
T25: 0.64 mg/kg/d (female rats, mammary fibroadenomas, oral)

3.1.1. Carcinogenicity data

Acrylamide is genotoxic. It has induced tumours in mice and rats after oral administration. In one female mice study, the animals develop lung and skin tumours after two weeks dosing. In two long-term studies with rats, acrylamide has induced tumours in both sexes at several sites.

3.1.2. Acute exposure

Toxic effects are dependent upon duration, total dose, and rat of exposure. Effects of acute high-dose exposure may be delayed in onset for several hours and include somnolence, confusion, hallucinations, disorientation, ataxia, tremors, and possibly seizures with cardiovascular collapse. Peripheral neuropathy and other organ system involvement appear after 1 to 2 days. Encephalopathy may occur in severe acute poisonings. Single or cumulative doses of as little as 50 to 100 mg/kg can cause neurological deficits. Doses of greater than 300 mg/kg can cause severe CNS and cardiovascular effects acutely.

3.1.3. Industrial use

The major use of acrylamide is in production of polyacrylamide.

3.1.4. Conclusion

Acrylamide is acutely toxic, mutagenic and carcinogenic. There is experimental evidence demonstrating tumour formation in mice after two weeks of exposure. Acrylamide induces tumours at different tumour sites in rats and mice. Single exposure can cause neurological damage. These considerations support the inclusion of the substance on the “carcinogens” list in the Seveso II Directive.

3.2. DIAZOMETHANE (CAS No. 334-88-3; EC No. 206-382-7)

Current classification: Carc. Cat. 2; R 45
Acute toxicity: No exact LD50/LC50 data known but regarded as “very toxic” (Römpp-Chemielexikon). Lethal in cats after 10 min inhalation of 0.3 mg/l (2% solution in ether).
T 25: Not calculated; rough estimation shows "high potency".

3.2.1. Carcinogenicity

There are no studies with respect to the carcinogenic potential after single exposure yet such an effect cannot be excluded given the strong methylating activity of the substance and the results from studies with relative short exposure time.

There exist older studies in rats and mice after inhalation, skin application and subcutaneous injection (note that these tests were not carried out according to today’s standards):

– Inhalation**:**
12 mice were exposed twice per week (= 2x/w) to vapour (0.1 – 3.3 mg/ml in ether) for 3 min./exposure for 6 months. Multiple pulmonary adenomas occurred in 7/10 mice compared to 2/8 in controls. In a further inhalation test with 8 male mice (5 months 2x/w each 1.5 min.) no tumours were recorded. In a repeat experiment with 12 exposures all mice developed lung tumours whereas in controls 3 of 6 tumours were observed. 13 male rats were exposed 2x/w for 1.5 – 3 min. each for 4.5 up to 6 months (0.1 – 3.3 mg/l solved in ether). Of 7 exposed rats surviving 10 months 3 had lung adenomas, 1 in addition a lung carcinoma; no tumours after 11 months in control animals.

– Skin application**:**
12 mice were painted on dorsal skin with 2 – 3 drops of ethereal solution (0.1 – 3.3 mg/l 5x/w for 5 months); 8/8 animals dying between 5 – 12 months had lung adenomas. No controls were used.

– Subcutaneous injection**:**
10 mice were given 8 monthly injections of 0.1 ml ethereal diazomethane plus 4 monthly injections of 0.1 ml undiluted diazomethane. From the 9 surviving mice after 26 months 1 had a spindle cell sarcoma and 1 had multiple pulmonary adenomas. No controls were used.

3.2.2. Physicochemical properties

BP. –23°C; "very explosive" in liquid state or concentrated solutions, especially in contact with metals or rough surfaces.

3.2.3. Biological properties

Strongly irritating. Methylating agent reacting with compounds containing various forms of active hydrogen occurring in biological material; it binds directly to DNA. As a methylating agent diazomethane is a direct-acting mutagen; it was positive in S. cerevisiae, E. coli and other tests.

3.2.4. Current industrial use

Diazomethane is not manufactured industrially. The substance is produced in situ when used in laboratories as a methylating agent.

3.2.5. Conclusion

Diazomethane as a gas, liquid or highly concentrated solution is explosive, highly irritant, toxic and mutagenic. It is a medium to high potency carcinogen. The high volatility (gas) would exclude exposure of neighbourhood in the case of a release. There is no industrial manufacturing and marketing because its physical properties restrict its use to that of a laboratory chemical produced in situ. These considerations support the exclusion of the substance from the “carcinogens” list in the Seveso II Directive.

References

IARC monographs on the evaluation of the carcinogenic risk to man vol. 7, 223 – 230 (1974)

TRGS 102 ChemG/Rechtsnormen, Kühn-Birett: Merkblätter Gefährlicher Arbeitsstoffe, 71. Erg.Lfg. 2/94

MAK-Begründung, 1997, Gesundheitsschädliche Arbeitsstoffe, Wiley-VCH

Römpp-Chemielexikon, 1981, p. 931

3.3. 1,2-DIBROMO-3-CHLOROPROPANE (CAS No: 96-12-8; EC No: 202-479-3)

Current classification: Carc. Cat 2; R45, Mut. Cat 2; R46, T;R25
Acute toxicity: Toxic (rat male oral LD50 = 170 mg/kg)
T25: 0.15 mg/kg/d (male rats, nasal cavity, inhalation)

3.3.1. Carcinogenicity

1,2-Dibromo-3-chloropropane is genotoxic. It induces tumours in rats and mice, both after oral administration and after inhalation. After administration by gavage, the substance cause a significant increase of squamous cell carcinomas of the forestomach, both in rats and mice and adenocarcinomas of the mammary gland in female rats. In an inhalation study, it caused increased incidence of nasal cavity tumours and tumours of the tongue in both male and female rats and cortical adenomas in the adrenal glands of the females. In mice an increased incidence is induced of nasal cavity tumours and lung tumours in both sexes.

3.3.2. Acute exposure

1,2-Dibromo-3-chloropropane is a testicular toxicant in experimental animals and humans. It is a mild eye and mucus membranes irritant and CNS depressant and liver and renal toxicant.

3.3.3. Industrial use

Commercial production of 1,2-dibromo-3-chloropropane is believed to have ceased world wide. The substance has been used as a pesticide, nematocide and soil fumigant.

3.3.4. Conclusion

1,2-dibromo-3-chloropropane is acutely toxic and mutagenic. It has induced tumours in both mice and rats after oral administration and inhalation exposure. These considerations support the inclusion of the substance on the “carcinogens” list in the Seveso II Directive.

3.4. 1,2-DIMETHYLHYDRAZINE (CAS No. 540-73-8)

Current classification: Carc. Cat 2: R45 T:R23/24/25
Acute toxicity: Toxic (rat oral LD_{50}:100 mg/kg; rat 4-hour LC_{50}: 0.7 mg/l)
T25: 0.022 mg/kg/day (high potency)

3.4.1. Carcinogenicity

There is experimental evidence to show that 1,2-dimethylhydrazine has the potential to produce cancer following a single exposure. A group of 28 male rats was administered a single oral dose of 35 mg/kg 1,2-dimethylhydrazine as the hydrochloride salt; a group of 14 control rats received the vehicle only (*Schiller et al.,1980*). All animals were maintained without further treatment for 18 months, at which time gross examination of liver, intestinal tract, kidney, lymph nodes and Zymbal's glands was performed. A total of 22/28 (79%) treated rats developed tumours, primarily in the colon (21/28 rats) compared with 0/14 controls.

3.4.2. Biological properties

Requires metabolic activation for expression of mutagenicity

3.4.3. Current industrial use

Unfortunately we have no information on industrial use. Secondary sources of information indicate it is used as a rocket propellant. However, it is not listed on the IUCLID database which suggests it is not a high tonnage chemical in the EU.

3.4.4. Conclusion

1,2-dimethylhydrazine is acutely toxic and mutagenic, and a high potency carcinogen. There is experimental evidence indicating the potential for 1,2-dimethylhydrazine to cause cancer following a single exposure at exposure levels considerably lower than those required to produce lethality. These considerations support the inclusion of this substance on the "carcinogens" list in the Seveso II Directive.

References

Schiller CM, Curley WH, McConnell EE (1980) Induction of colon tumours by a single oral dose of 1,2-dimethylhydrazine. Cancer Letters, 11, 75-79

3.5. DIMETHYL SULPHATE (CAS No. 77-78-1; EC No. 201-058-1)

Current classification: Carc Cat 2; R45 T+:R26 C:R34
Acute Toxicity: Very Toxic (rat 4-hour LC_{50}:0.045 mg/l (HSE, 1996a))
T25: 0.05 mg/kg/day (high potency)

3.5.1. Carcinogenicity

There is some evidence to suggest dimethyl sulphate could produce tumours following a single exposure, although this aspect has not been systematically investigated and the evidence is not entirely clear. Local tumours (sarcomas) at the site of injection developed in 7/15 rats following a single subcutaneous injection of 50 mg/kg. No control group was included, although it was reported that the vehicle used did not produce local tumours at the injection site (IPCS, 1985). However, the induction of local tumours at the site of injection is of doubtful relevance to the assessment of carcinogenic hazard in humans, hence this evidence is not convincing for the potential to cause tumours in humans following a single exposure.

A single intravenous injection of 75-150 mg/kg dimethyl sulphate failed to produce tumours in rats, whereas renal carcinomas developed after similar treatment with methylnitrosourea and dimethylnitrosamine.

Groups of mice, rats and hamsters were exposed by inhalation to 20 mg/m3 (mice and rats) or 48 mg/m3 (hamster) dimethyl sulphate for 4 x 1-hour periods 4 times per year. The results indicated some suggestion of an increase in malignant tumours compared to controls in rats only. Malignant tumours (no further details available) developed in single animals in the lung, nose and eye, compared to a zero incidence of these tumours in control animals. Other studies indicate that following repeated inhalation exposure in rodents, dimethyl sulphate produces tumours primarily in tissues at the site of contact (nasal tract and lungs).

In a limited study of transplacental carcinogenicity, 8 pregnant rats were administered a single dose of 20 mg/kg dimethyl sulphate on day 15 gestation. The 59 offspring were observed for more than one year and of these, 7 developed malignant tumours, including three tumours of the brain.

3.5.2. Biological properties

Direct acting mutagen; powerful methylating agent; reacts predominantly with N-7 of guanine (IPCS 1985). Covalent Binding Index: 37 (4-hours after i.v. dose, in rat liver, cf. 7100 for dimethylnitrosamine, 5-hours after i.p. dose or 400 for N-methyl-N-methylnitrosourea, 4-hours after i.v. or oral dose).

3.5.3. Current industrial use

A survey conducted in 1994 revealed that total usage in the UK was around 4500 tonnes per annum (HSE 1996a). It was understood that some 55 companies used dimethyl sulphate in industrial processes in Great Britain, mainly as a methylating agent in organic chemical syntheses, a quaternizing agent in the manufacture of dyestuffs and detergents, and in the production of pharmaceuticals. Current usage is likely to be lower than in 1994, but no current information is immediately available.

3.5.4. Conclusion

Dimethyl sulphate is acutely toxic and mutagenic, and is carcinogenic primarily in tissues at the site of contact. The results of carcinogenicity studies in animals, including a study of transplacental carcinogenicity, support the view that this substance may have some potential to produce tumours in humans following a single exposure. These considerations support the inclusion of this substance on the “carcinogens” list in the Seveso II Directive.

References

Druckrey H, Nashed N, Preussman R et al (1970) Cancerogenic alkylating substances III Alkyl-halogenenides, -sulphates, -sulfonates and strained heterocyclic compounds Z. Krebforsch 74, 24-273

IPCS (1985) Environmental Health Criteria: Dimethyl sulphate. WHO, Geneva.

MAK Documentation. DFG Deutsche Forschungsgemeinschaft. Occupational Toxicants. Critical Evaluation for MAK Values. Vol 4. 1992, pp 217-223

HSE (1996a) Dimethyl and diethyl sulphates. Criteria document for an occupational exposure limit. HSE Books. EH65/27 ISBN 0-7176-1058-6

3.6. 2-METHYLAZIRIDINE *(Propyleneimine or 2-Methylazacyclopropane)* (CAS No. 75-55-8, EC No. 200-878-7)

Current classification: Carc. Cat. 2; R45. T+; R26/27/28. F; R11. Xi; R41. N; R51-53

Acute toxicity: Very toxic. Oral rat LD50=19 mg/kg. Inhalation-rat LCLo=500 ppm/4h, Inhalation guinea pig LCLo=500 ppm/1h. Skin guinea pig LD50= 43 mg/kg (SAX's, 1992)

T25: ca. 0.8 mg/kg bw/day

3.6.1. Carcinogenicity

2-methylaziridine has been classified as IARC-2B (IARC, 1999), as EC Carc.Cat.2, and agreed by EC to be a High Potency Carcinogen.

2-methylaziridine was considered by working groups of the International Agency for Research on Cancer (IARC) in 1975, in the updating in 1987, and recently in 1999. It was evaluated as follows: "There is *sufficient evidence* for the carcinogenicity of 2-methylaziridine to animals. No epidemiological data relevant to the carcinogenicity of 2-methylaziridine to humans were available. *The agent is possibly carcinogenic to humans* (*Group 2B*)".

Recently (January 2000) 2-methylaziridine was agreed to be a High Potency Carcinogen by the Commission Working Group on the Classification and Labelling of Dangerous Substances (Directive 67/548/EEC).

Animal Data: Oral administration of 20 and 10 mg/kg bw of 2-methylaziridine to rats twice a week for 28 and 60 weeks, respectively, induced mammary adenocarcinomas in females (10/26 and 21/26 compared with 0/16 in the controls) and granulocytic leukaemia in males (6/26 and 4/26 compared with 0/16 in the controls). There was a small, but not significant increase in frequency of malignant gliomas, ear duct squamous cell carcinomas and intestinal adenocarcinomas (Weisburger, 1981).

Mutagenic and Genotoxic Information: 2-methylaziridine was mutagenic to Salmonella typhimurium and modified DNA in Escherichia coli (Rosenkranz, 1979). It induced mitotic recombinations in Saccharomyces cerevisiae (Simmon, 1979) and cell transformation in three different mammalian cell systems (Dunkel, 1981).

Human Data: No references were identified in a literature review. No epidemiological data were available to the IARC working groups in 1975, 1987, and 1999.

3.6.2. Physicochemical properties

2-methylaziridine is a liquid. Vapour density 2.0. Flash point $-4^{o}C$

It is a poison by ingestion and skin contact. It is very toxic by all routes of exposure. Severe eye irritant. A very dangerous fire hazard when exposed to heat of flame; can

react vigorously with oxidising materials. Polymerises explosively on exposure to acids or acid fumes. When heated to decomposition it emits toxic fumes of NOx.

OSHA PEL and ACGIH: TLV-TWA 2 ppm (skin). NIOSH: IDLH=500 ppm

3.6.3. Current industrial use

The main use of 2-methylaziridine is as an intermediate in chemical syntheses used in the modification of dyes and polymers (IARC, 1975).

3.6.4. Conclusion

2-Methylaziridine is a recognised animal carcinogen regarded as if carcinogenic to human, but there is no evidence to suggest that it can be a single exposure carcinogen. It is classified as "Very Toxic", and therefore comes under the Seveso II Directive with qualifying quantities of 5/20 tonnes. In the event of an accident involving methylaziridine, the dominant concern would be acute toxicity. These considerations support the exclusion of the substance from the "carcinogens" list in the Seveso II Directive.

References

IARC (1975) IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man. Vol. 9. Some aziridines, N'-S'- and O-mustards and selenium, Lyon, 61-65

IARC (1987) IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Supplement 7. Overall evaluation of carcinogenicity. An updating of IARC Monographs Vol. 1 to 42, Lyon, 66

IARC (1999) IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Vol. 71, Lyon, p. 1497.

Weisburger, E.K., Ulland, B.M., Nam, Jun-mo., Gart, J.J. and Weisburger, J.H. (1981) Carcinogenicity tests of certain environmental and industrial chemicals. *J. natl Cancer Inst.,* **67,** 75-88

Rosenkranz, H.S. and Poirier, L.A. (1979) Evaluation of the mutagenicity and DNAmodifying activity of carcinogens and noncarcinogens in microbial systems. *J. natl Cancer Inst.,* **62,** 873-892

Simmon, V.F. (1979) *In vitro* assays for recombinogenic activity of chemical carcinogens and related compounds with *Saccharomyces cerevisae* D3. *J. natl Cancer Inst.,* **62,** 901-909

Dunkel, V.C., Pienta, R.J., Sivak, A. and Traul, K.A. (1981) Comparative neoplastic transformation responses of Balb/3T3 cells, Syrian hamster embryo cells and Rauscher murine leukaemia virus-infected Fischer 344 rat embryo cells to chemical carcinogens. *J. natl Cancer Inst.,* **67,** 1303-1315

CEC – Berlin A., Draper M., Krug E., Roi R., Van der Venne M.Th. (eds) (1989) The toxicology of chemicals. 1-Carcinogenicity. Summary reviews of the scientific evidence. Vol. I, 153-154. EUR 12029 EN, ISBN 92-825-9381-9.

Patnaik P. (1992) A Comprehensive Guide to the Hazardous Properties of Chemical Substances, pp. 166-167, Van Nostrand Reinhold, ISBN 0-442-00191-6.

Lewis R.J. Sr. (1992) Sax's Dangerous Properties of Industrial Materials, 8th ed., Vol.III, Van Nostrand Reinhold, ISBN 0-442-01278-0.

3.7. 4-METHYL-M-PHENYLENEDIAMINE *(Toluene-2,4-diamine or TDA)* (CAS No 95-80-7; EC No 202-453-1)

Current classification: Carc Cat 2:R45 T:R25 Xn:R21 Xi:R36 R43 N:R51,53
Acute toxicity: Harmful (rat oral LD_{50} 230-270 mg/kg)
T25: 1.3 mg/kg/day

3.7.1. Carcinogenicity

The majority of carcinogenicity studies are lifetime feeding studies. The main tumour finding is liver carcinoma. However, when dietary exposure was terminated after 60 days, the liver changes regressed. This indicates that 4-methyl-m-phenylenediamine induced liver damage is reversible following cessation of exposure. This suggests that any damage following a single exposure would also be reversible and unlikely to lead to tumour development.

3.7.2. Biological properties

Requires metabolic activation for the expression of mutagenicity. Equivocal evidence for *in vivo* mutagenicity; equivocal evidence for DNA binding *in vivo*.

3.7.3. Current industrial use

4-methyl-m-phenylenediamine is produced in Europe in an amount of about 350,000 t/y. Is practically used to 100% as intermediate in production of TDI.

3.7.4. Conclusion

The potential for 4-methyl-m-phenylenediamine to produce cancer following a single exposure has not been specifically investigated. Following repeated dietary exposures it is a liver carcinogen in rodents, but the mechanism of liver tumour formation may involve chronic liver damage. There is evidence that the liver damage produced by 4-methyl-m-phenylenediamine is reversible on cessation of exposure. Overall, the available evidence does not support the view that 4-methyl-m-phenylenediamine has the potential to cause cancer following a single exposure. These considerations support the exclusion of the substance from the “carcinogens” list in the Seveso II Directive.

References

MAK Documentation. DFG Deutsche Forschungsgemeinschaft. Occupational Toxicants. Critical Evaluation for MAK Values. Vol 6 1995, pp339-352

3.8. DIETHYL SULPHATE (CAS No 64-67-5; EC No 200-589-6)

Current classification: Carc Cat 2:R45; Muta Cat 2: R46; Xn:R20/21/22; C:R34
Acute toxicity: Harmful (rat oral LD_{50} 880 mg/kg; rat 4-hr inhalation 0% mortality at 1.6 mg/m3, 100% mortality at 3.2 mg/m3 (HSE 1996a))
T25: ca. 3 mg/kg/day (old data)

3.8.1. Carcinogenicity

There are no carcinogenicity studies using the inhalation route. In an oral gavage study groups of 12 rats were administered 25 or 50 mg/kg weekly for 81 weeks (*Druckrey et al 1970*). One rat per dose developed a squamous carcinoma of the forestomach and benign forestomach papillomas were observed in 6/24 animals. However, there were no controls. In a skin painting study (cited in HSE 1996), mice were treated with ~7.4 mg 3x per week for life (or until malignant tumours developed). Malignant skin tumours developed in 21 animals, with none in control animals. Stomach tumours also developed in 5 treated animals, presumably due to licking the diethyl sulphate from the skin. The first tumour appeared at 12 months.

In a study to investigate transplacental carcinogenicity, 3 rats were administered a single subcutaneous injection of 85 mg/kg diethyl sulphate on day 15 gestation (*Druckrey 1973*). It is not clear if controls were included. Tumours of the nervous system developed in 2/30 offspring. The historical control incidence for nervous system tumours was reported to be less than 0.1%.

3.8.2. Biological properties

Direct acting mutagen. Positive genotoxicity data *in vivo* in somatic and germ cells.

3.8.3. Current industrial use

We have no information on the current industrial use of diethyl sulphate within Great Britain, but a survey conducted in 1994 revealed that total usage in the UK was around 1000 tonnes per annum (HSE 1996). It was stated that it was largely imported from the USA, but some was imported from Japan via storage in Rotterdam. It is likely that current usage may be lower than in 1994. The principle use of diethyl sulphate in industrial processes in Great Britain is as an ethylating agent in dyestuffs and pharmaceuticals manufacture.

3.8.4. Conclusion

Diethyl sulphate is acutely toxic and a direct acting mutagen, and in view of the development of tumours in the offspring of animals administered a single dose of diethyl sulphate, this substance should be regarded as having some potential to cause tumours following a single exposure. These considerations support the inclusion of this substance on the “carcinogens” list in the Seveso II Directive.

References

Druckrey H, Nashed N, Preussman R et al (1970) Cancerogenic alkylating substances III Alkyl-halogenenides, -sulphates, -sulfonates and strained heterocyclic compounds Z. Krebforsch 74, 24-273

Druckrey H, Gimmy J and Landschdtz C (1973) Cancerogenicity of di-isopropylsulfate and non-cancerogenicity of monomethylsulpate in bd-rats. Z.Krebforsch 79, 13-140

HSE (1996a) Dimethyl and diethyl sulphates. Criteria document for an occupational exposure limit. HSE Books. EH65/27 ISBN 0-7176-1058-6

3.9. BENZOTRICHLORIDE (CAS No: 98-07-7; EC No: 202-634-5)

Current classification: Carc. Cat 2; R45, T;R45-22-23-37/38-41
Acute toxicity: Toxic (mice inhalation, LC50 = 60 mg/m^3, 7.9 mg/kg)
T25: 0.02 mg/kg/d (female mice, lung tumours, inhalation)

3.9.1. Carcinogenicity data

Epidemiological data suggest that benzotrichloride may be a human lung carcinogen. Benzotrichloride has induced tumours in mice after oral administration, skin painting and inhalation exposure. It is a bacterial mutagen.

3.9.2. Acute exposure

Benzotrichloride vapour is highly irritant to skin and mucous membranes.

3.9.3. Industrial use

Benzotrichloride is mostly used as a chemical intermediate, primarily for benzoyl chloride. Lesser amounts are used in the manufacture of benzotrifluoride as a dyestuff intermediate and in producing hydroxybenzofenon ultraviolet light stabilizers. In the EU the production volume in 1999 was between 15,000 and 20,000 tonnes.

3.9.4. Conclusion

Benzotrichloride is acutely toxic and a bacterial mutagen. It has induced tumours in both mice and rats after oral administration, skin painting and inhalation exposure. These considerations support the inclusion of the substance on the “carcinogens” list in the Seveso II Directive.

3.10. HYDRAZINE (CAS No 302-01-2; EC No 206-114-9)

Current classification: R10 Carc Cat 2:R45 T:R23/24/25 C:R34 R43
Acute Toxicity: Toxic (rat oral LD_{50}:60 mg/kg; rat 4-hr LC_{50} ~0.75 mg/l, mouse 4-hr LC_{50} ~0.33 mg/l, HSE 1996b)
T25: 1 mg/kg/day

3.10.1. Carcinogenicity

There are no studies which have investigated the single dose carcinogenic potential of hydrazine, but there is a recent study involving a limited number of brief inhalation exposures. Groups of 100 rats/sex and 100 male hamsters were exposed to 0, 75 or 750 ppm hydrazine for 1 hour per day, 1 day per week for 10 consecutive weeks. Animals were then maintained without further exposure for 22 months (hamsters) or up to 28 months (rats). There was no treatment-related effect on mortality, and only slight reductions in body weight gain in rats and hamsters at 750 ppm, and in female rats only at 75 ppm, which returned to control values post-exposure. The only significant treatment-related lesions were in the nasal cavity. In both species at 750 ppm there was a statistically significant increase in the incidence of hyperplasia of the transitional epithelium (2-3%) and of polyploid adenoma (3-5%) in the nasal cavity. One male rat had a squamous cell carcinoma in the nasal cavity. In hamsters there was an adenoma of the Bowman's glands and a neuroblastoma, again both in the nasal cavity. At 75 ppm, proliferative lesions of the nasal cavity were seen in 2/94 male rats and 1/93 hamsters, one of these (in the rat) was a squamous cell carcinoma. No proliferative lesions were seen in the nasal cavity of control animals. It was also shown that in rats and hamsters exposed once for 1-hour to 750 ppm, severe necrotic and apoptotic changes were produced in the same region of the nasal cavity, 24 hours after exposure.

Furthermore, there are a large number of repeated exposure carcinogenicity studies conducted largely with hydrazine sulphate indicating that hydrazine is carcinogenic in the nasal cavity of rats and hamsters following inhalation exposure, and in the liver of hamsters following exposure via the drinking water. There was also evidence for malignant tumours in the colon of hamsters following inhalation exposure at 5 ppm 6 hours/day, 5 days week for 6 months.

3.10.2. Biological properties

Genotoxic *in vitro*, with and without metabolic activation; *in vivo* mutagenicity not adequately investigated. Methylating agent, at O6 and N-7 of guanine; mechanism may be indirect, i.e. cytotoxicity rather than direct binding to cellular DNA.

3.10.3. Current industrial use

Hydrazine is a liquid mainly used as a hydrate with a maximum hydrazine concentration between 15 and 64%. The vapour tension is low, which reduces the possibility of exposition to toxic vapours. Its anhydrous form is used as a fuel in the rocket industry.

According to CEFIC in Europe the production volume is between 20,000 and 25,000 t/y. About 90% of this tonnage are used as intermediates, about 10% for corrosion protection in boiler water treatment.

An HSE review in 1996 revealed that hydrazine is not manufactured in Great Britain, but at that time was imported in quantities corresponding to about 1000 tonnes of hydrazine hydrate annually, from manufacturing sites in France and Germany. About half was used in boiler water treatment. Most of the remainder is used in chemical synthesis mainly in the agrochemical and pharmaceutical industries. It is not known whether the industrial usage pattern in Great Britain has changed significantly since that time. Annual production volumes are reported of 640,000 tonnes from Germany and 600,000 tonnes in France. Information from Austria indicates that hydrazine is used in thermal power stations (public energy supply and industrial installations) as a corrosion inhibitor agent. In Austria it is estimated that ca. 10-15 large combustion plants use hydrazine, and a considerable number of smaller plants also use hydrazine for corrosion protection. The typical amounts of hydrazine (15% solution) present in establishments are:

- up to 100 kg in smaller plants
- up to 700 kg in larger plants.

It is envisaged that hydrazine will continue to be used in future as it is difficult to switch to the alternative combined technology using ammonia and oxygen.

3.10.4. Conclusion

Hydrazine is acutely toxic and mutagenic. Following inhalation exposure it is carcinogenic mainly in tissues at the initial site of contact (respiratory tract), with evidence for tumour induction in two animal species following only a very limited number of short exposures. Furthermore, there is evidence for single-exposure carcinogenicity with a closely related compound (1,2-dimethylhydrazine). In view of this pattern of evidence, hydrazine should be regarded as having the potential to cause cancer in humans following a single exposure. These considerations support the inclusion of the substance on the “carcinogens” list in the Seveso II Directive.

References

HSE (1996b) Hydrazine. Criteria Document for an occupational exposure limit. HSE Books. EH65/28 ISBN 0-7176-1099-3

Latendresse JR, GB Marit, EH Vernot, CC Haun and CD Flemming (1995) Oncogenic potential of inhaled hydrazine in the nose of rats and hamsters after 1 or 10 1-hour exposures. Fund Appl Toxicol, 27; 33-48

3.11. EPICHLOROHYDRIN (CAS No. 106-89-8; EC No. 203-439-8)

Current classification:	R 10; Carc. Cat. 2: R 45; T, 23/24/25-34-43
Acute toxicity:	Rat oral LD50 90 – 260 mg/kg bw; dermal mouse LD50 250 mg/kg bw; dermal rabbit 754 – 1,038 mg/kg bw; rat inhalation 500 ppm = 2 mg/l/6 h
T25:	Not exactly calculated, yet greater than 1 mg/kg bw/day (TDX 40 mg/kg bw/d).

3.11.1. Carcinogenicity

Epichlorohydrine was tested for carcinogenicity in several species by different exposure routes. Furthermore, there are two case studies in man which both give no sufficient evidence for a carcinogenic potency.

Oral administration:

Rats were exposed to drinking water containing to 0, 375, 750, 1.500 mg/l (ppm) epichlorohydrine with unspecified purity for 81 weeks. Hyperplasia, papilloma to carcinoma occurred in incidences increasing with dose in the forestomach. Tumors at other sites were not observed. - In another study rats were administered 0, 2, 10 mg/kg bw epichlorohydrine by gavage on 5 d/w over 2 years. Incidence of forestomach hyperplasia, papilloma and carcinoma was increased in both sexes (carcinoma 0/50; 6/49; 35/49 in males and 0/50; 2/44; 24/39 in females).

Inhalation exposure:

Rats were exposed by whole-body inhalation to 0, 10, 30 ppm (0, 38, 113 mg/m³) 6 h/d on 5 d/w for life-time. Two further groups were exposed to 100 ppm for 6 h/d on 30 days followed by life-time observation. In the 10 ppm group no neoplastic changes were reported. In the 30 ppm group one rat had a nasal papilloma and one a squamous cell carcinoma of the nasal cavity. In rats exposed 30 times to 100 ppm and observed for life-time, 17 rats (total 140) developed 15 squamous cell carcinomas and 2 papillomas of the nasal epithelium; furthermore, one bronchial papilloma and 4 pituitary adenomas as well as squamous cell carcinoma in the forestomach were observed. No tumor of these types were found in controls.

Intraperitoneal administration:

After intraperitoneal injection 3 x/w for 8 weeks of total doses of 20, 50 and 100 mg/kg bw significantly increased number of lung tumors in male mice treated with 100 mg/kg were observed but no tumors in other groups. In an other experiment in mice given weekly i.p. injection of 1 mg epichlorohydrine for 450 d 7/30 developed papillary tumors of the lung. 10/30 control animals treated with the solvent tricaprylin alone developed also lung tumors.

Skin application:

Mice painted 3 x/w with undiluted epichlorohydrine showed no tumors after treating for life-time. In a second study with dermal application of 2 mg 3 x/w no skin tumors were observed after life-time exposure.

In an initiation/promotion study with single doses of 2 mg epichlorohydrine dissolved in acetone whereby 2 weeks later treatment with phorbol myristate followed 3 x/w for 385 d, 1/30 mice developed a skin carcinoma and 9 mice skin papillomas.

Subcutaneous administration:

Local sarcomas were observed after 300 days after weekly injection of 1 mg epichlorohydrine in 2/50 mice. In a similar study (duration 580 d) 6/50 mice and 1/50 developed local sarcomas and local adenocarcinoma, respectively, after weekly s.c. injection of 1 mg epichlorohydrine.

3.11.2. Physicochemical properties

Boiling Point 115 - 117°C by 13 hPA; vapor pressure 13 – 17 hPA at 20°C; water solubility: 65 g/l at 20°C.

3.11.3. Biological properties

Epichlorohydrine is genotoxic in several in vitro systems and also positive in vivo in mouse micronucleus test, UDS sperm head morphology and mammalian germ cell cytogenetic assay in mouse, whereas some other tests, e.g. DL test and cytogenetic assays were negative. The substance has a high potential for irritation and corrosive activity, respectively. It is toxic by all relevant exposure routes.

3.11.4. Conclusion

Epichlorohydrine is toxic, irritative/corrosive and mutagenic in vitro and in vivo in soma cells without metabolic activation.

Following inhalation and oral exposure it is carcinogenic in tissues at the initial site of contact (respiratory tract; forestomach). Negative results were observed after skin painting in mice, yet epichlorohydrine was active as an initiator on skin. From human studies there is inadequate evidence for carcinogenicity. Based on all study results the carcinogenicity potency is not regarded as high; in Germany it was classified in group III.

In conclusion, this substance has a T25 value greater than 1 mg/kg/day. It is classified as Toxic and therefore is already subject to the requirements of the Seveso II Directive (qualifying quantities 50/200 tonnes). On that ground the group decided to exclude it from the list.

References

IARC Monographs 11, 131 – 139 (1976); Vol. 71, part 2, 603 – 628 (1999)

TRGS 102; Arbeits-/Gesundheitsschutz, Kühn, Birett, Erg.Lfg. 9/1992, page 29.

3.12. 4,4'-DIAMINODIPHENYLMETHANE *(4,4'-methylene dianiline or "MDA")* (CAS No 101-77-9; EC No 202-974-4)

Current classification: Carc Cat 2 R45 Xn: R20/21/22, 48/20/21 R43 N:R51,53
Acute toxicity: Harmful (rat oral LD_{50} 355-830 mg/kg (HSE 1993)
T25: 6.2 mg/kg/day

3.12.1. Carcinogenicity

MDA produces liver and thyroid tumours in rats and mice following repeated oral administration (HSE 1993). However, at the same dose levels producing tumours, MDA also produces chronic tissue damage in the liver and hyperplasia in the thyroid. Given that there is a lack of clear evidence for the *in vivo* mutagenicity of MDA, it is possible that the tumours arose as a consequence of chronic tissue damage (liver) and tissue-stimulating (thyroid) effects, but overall the mechanism(s) involved in tumour development in rats and mice are uncertain.

There are no studies in which tumour development has been investigated following single exposures. However, there are some poor quality studies cited in HSE documentation (1993) in which a limited number of individual doses were administered to rats or mice. Two of these studies did not include control groups and do not allow any reliable conclusions to be drawn. The remaining study involved administration to 20 rats of 10 oral doses of MDA at the maximum tolerated dose (30 mg). There were 140 vehicle control animals. Animals were sacrificed 9 months post-treatment, and no significant non-neoplastic or tumour findings were observed.

3.12.2. Biological properties

Requires metabolic activation for the expression of mutagenicity. *In vivo* genotoxicity not well investigated and picture uncertain. Negative results were obtained in an *in vivo/in vitro* liver UDS assay in rats. Positive results have been reported for SCE and micronucleus formation in mice following intraperitoneal administration, but the significance of these results (briefly reported study with few experimental details provided) for physiological routes of exposure is uncertain.

3.12.3. Current industrial use

MDA is produced in Europe in amounts of 400,000 – 500,000 t/y. More than 90% are used in the preparation of MDI; further uses are hardener resins and adhesives.

In a survey conducted in 1991 by HSE it was estimated that about 51,000 tonnes of MDA were manufactured in Great Britain per annum. About 95% of the crude MDA was used to make methylene diphenyl-di-isocyanate and the remainder used as a curing agent in a wide range of epoxy-resin and some polyurethane elastomer systems. We have no information on whether current manufacture and use patterns have changed.

3.12.4. Conclusion

While MDA is a clear mutagen in vitro, it is uncertain whether it should be regarded as an in vivo mutagen. MDA is a carcinogen in rats and mice following repeated oral exposure but the mechanism(s) of tumour development are uncertain, and it is possible that the tumours produced by MDA arise as a consequence of chronic liver damage and repeated thyroid stimulation. Overall, there is no evidence to indicate that MDA has the potential to cause cancer in humans following a single exposure incident. These considerations support the exclusion of the substance from the “carcinogens” list in the Seveso II Directive.

References

HSE (1993) 4, 4’-Methylene dianiline. Criteria Document for an occupational exposure limit. HSE Books. EH65/5 ISBN 0-11-882083-4

3.13. 1,2-DIBROMOETHANE (CAS 106-93-4; EC No: 203-444-5)

Current classification:	Carc 2; R45, T; R23/24/25, Xi; R36/37/38, N; R51/53
Acute toxicity:	LC_{Lo} (rat) 3.12 mg/l; LD_{50}(rat, oral) 108-146 mg/kg; LD_{50}(rabbit, dermal) 300 mg/kg *(EU-classification scheme - June 1984)*
T25:	2.5 mg/kg/d (Sanner 1999)
IARC:	Probably carcinogenic to humans (group 2A)

3.13.1. Carcinogenicity

Only few epidemiological studies have been conducted with either few people or with multiple exposures to various pesticides, thus no conclusion with respect to carcinogenicity of dibromoethane from these data could be drawn (IPCS 1997; IARC 1999).

Following oral administration dibromoethane produced squamous-cell carcinomas of the forestomach in rats and mice, an increased incidence of alveolear/bronchiolar lung tumours in mice of each sex, haemangiosarcomas in male rats, and oesophageal papillomas in female mice. Following inhalation dibromoethane produced adenomas and carcinomas of the nasal cavity, haemangiosarcomas, mammary gland tumours, subcutaneous mesenchymal tumours, an increased incidences of alveolear/bronchiolar lung tumours in mice and rats and an increased incidence of peritoneal mesotheliomas in male rats. The substance induced skin and lung tumours in mice after skin application.

Dibromoethane has been found to be genotoxic in a broad range of in-vitro and in-vivo assays and binds covalently with DNA after exposure in rodents in-vivo.

The US EPA has estimated a 10^{-4} lifetime risk for cancer at an average exposure level of 5×10^{-4} mg/m^3 (unit risk estimate: 2.2×10^{-4} (ug/m^3)$^{-1}$.

3.13.2. Other toxic properties

Dibromoethane is strongly irritant to the eyes, skin, and respiratory tract. Inhalation exposure to concentrations over 215 mg/m^3 (20 ppm) for more than 30 min is considered fatal to humans (IPCS 1997).

Investigations in different mammalian species as well as epidemiological studies have shown that exposure to 1,2-dibromoethane can cause adverse effect in the respiratory tract, the nervous system and in the kidneys. Furthermore exposure to the substance has resulted in reduced fertility, testicular atrophy, impairment of sperm quality and reduction in sperm count.

3.13.3. Industrial use

The production capacity of 1,2-dibromoethane in Western Europe amounts to about 45,000 tonnes per year. The substance is only produced in France and Great Britain (and

up to 1986 in the Federal Republic of Germany). Dibromoethane is (has) mainly been used for a lead scavenger additive in leaded gasoline and as a storage insecticide and soil fumigation agent. Furthermore small amounts are used as chemical intermediate and as a solvent.

3.13.4. Conclusion

Dibromoethane is a genotoxic and potent carcinogenic substance producing multiple tumours at various organ sites in experimental animals. Based on these data dibromoethane should be considered as a one-shot carcinogen. These toxicological considerations support the inclusion of the substance on the list named carcinogens in the Seveso II Directive.

References

BUA (1991). 1,2-dibromoethane. BUA report 66. Gesellschaft Deutscher Chemiker.

IARC (1999). Ethylene dibromide. In: IARC Monographs on the evaluation of carcinogenic risks to humans vol 71 (part two), Reevaluation of some organic chemicals, hydrazine and hydrogen peroxide, 641-670.

IRIS (1997). Database of the U.S. Environmental Protection Agency. Chem-Bank. Silverplatter information, Health & Safety Publishing.

IPCS (1997). 1,2-dibromoethane. Environmental Health Criteria 177. International Programme on Chemical Safety, WHO, Geneva.

3.14. METALS: Compounds of Beryllium, Cadmium, Chromium and Cobalt.

Current classification:
Beryllium compounds: Carc. Cat 2: R49, T+: R26, T: R25-48/23, Xi: R36/37/38, R43, and N: R51-53

Cadmium compounds: Xn: R20/21/22, N: R50-53.

However, some compounds do have an additional stronger classification:
cadmium formate, cadmium hexafluorosillicate, cadmium iodide:
T: R23/25
cadmium oxide, cadmium sulphate:
Carc. Cat 2: R49, T: R48/23/25;
cadmium sulphide: Carc. Cat 3: R40, T: R48/23/25;
cadmium cyanide: T+: R26/27/28;
cadmium chloride, cadmium fluoride:
Carc. Cat 2: R45, T+: R26.

Chromium compounds:
chromium (VI) compounds: Carc. Cat 2: R49, R43, N: R50-53.

However, some compounds do have an additional stronger classification:
chromium trioxide: Carc. Cat 1: R49, T: R25, O: R8;

Cobalt compounds:
cobalt dichloride, cobalt sulphate:
Carc. Cat 2: R49, Xn: R22, R42/43 and N: R50-53;
cobalt oxide: Xn: R22, R43;
other cobalt compounds have not been classified.

3.14.1. Carcinogenicity

IARC has classified beryllium and beryllium compounds, cadmium and cadmium compounds and chromium (VI) compounds as Group 1 carcinogens (The agent (mixture) is carcinogenic to humans). Cobalt and cobalt compounds are classified as Group 2B (The agent (mixture) is possibly carcinogenic to humans). Lung cancer has been found after occupational exposure to beryllium and beryllium compounds, cadmium and cadmium compounds and chromium (VI) compounds. Cancer formation in humans appears only to be induced after occupational exposure for several years.

Animal carcinogenicity data for compounds belonging to these four metals are limited. Inductions of tumours have in most cases not been found after oral administration. Single dose carcinogenic data by administration routes relevant for humans on these compounds are absent. The mechanism of carcinogenicity for most metals and metal compounds suggests that they would not be single exposure carcinogens. (Both human occupation exposure and animal inhalation exposure have shown that most of the substances are high potency carcinogens.)

3.14.2. Current industrial use

There is limited information on the current industrial use of compounds of these four metals. However, most of the metal compounds specified above are used in very limited quantities in industry today. Some data is available for cobalt sulphate (used primarily in animal feed, electroplating, anodising, copper electrowinning and recording tapes) for which the total EU consumption is reckoned at 1,430 tonnes of compound, and for cadmium chloride, for which European usage is reckoned at < 1000 tonnes.

3.14.3. Conclusion

A short review of the toxicological data for these metal compounds have not showed any new scientific data that suggests that these are single exposure carcinogens. These considerations support the exclusion of these substances from the “carcinogens” list in the Seveso II Directive.

4. INVESTIGATIONS ON SUBSTANCES IN THE EXISTING "CARCINOGENS" LIST

For the reasons mentioned in Chapter 2, it is proposed to retain all these substances in the new list of 'carcinogens'.

4.1. 4-AMINOBIPHENYL (*CAS No. 92-67-1; EC No. 202-177-1*) and/or salts

Current classification:	Carc. Cat 1: R45, Xn: R22
Acute toxicity:	Harmful
T25:	DC (5, 38w; Insufficient data to calculate T25)

4.1.1. Properties

4-aminobiphenyl is a colourless crystalline solid, m.p. 53ºC and b.p. 302ºC. Slightly soluble in water but soluble in alcohol, ether and chloroform.

4.1.2. Carcinogenicity

After long-time exposure, it produces cancer in mice, dogs and rabbits after oral intake, and liver tumours in mice after oral and intraperitoneal administration. The hydrochloride induces bladder and liver tumours in mice after oral administration. It is mutagenic to bacteria and mutagenic and DNA damaging in cultured mammalian cells. It induces bladder tumours in humans. In the epidemiological studies, confined to one series of workers occupationally exposed to commercial 4-aminobiphenyl, a high incidence of bladder carcinomas was reported. In consequence one can say that bladder cancer was strongly associated with occupational exposure to 4-aminobiphenyl. No information is available on effects to animals or man after short-time exposure, or environmental fate (except for solubility data above).

4.1.3. Industrial use

It was manufactured and used as a rubber antioxidant. It is not used in industry at present, but some of its salts are in use. Marketing and use for research purpose are restricted to professional users.

This compound is banned according to Directive 88/364/EEC with respect to production and use. The only exceptions, i.e. for scientific research and production as intermediate in closed systems, are not relevant from a practical point of view. The respective azo dyes which had been produced from these compounds in earlier times are not introduced or relevant in the EU anymore.

4.2. BENZIDINE (*CAS No: 92-87-5; EC No: 202-199-1*) and/or salts

Current classification: Carc. Cat 1: R45, Xn: R22, N: R50-53
Acute toxicity: Harmful
T25: 0.005 mg/kg/day (high potency)

4.2.1. Properties

Benzidine (1,1'-biphenyl-4,4'-diamine) is a white crystalline powder, m.p. 129ºC. It is only slightly soluble in water (0.4 g/l cold water) but soluble in ethanol and ether.

4.2.2. Carcinogenicity

Benzidine and its salts have during long-time tests produced liver tumours by oral administration in rats, mice and hamsters, and bladder tumours in dogs. No adequate inhalation studies are available. It is mutagenic to bacteria, yeast and eukaryotic cells in culture. It also induced sister chromatic exchange, chromosomal aberrations and cell transformation in eukaryotic cells in culture. In vivo it induced DNA damage, sister chromatic exchanges, chromosomal aberrations and micronuclei. A causal relationship has been established in humans between exposure to benzidine and development of malignant tumours of the bladder. No information is available on the effects to animals or man after short-time exposure, or environmental fate (except for solubility data above).

4.2.3. Industrial use

Benzidine has been the basic starting chemical for a group of dyes. Today, these dyes are synthesised in other ways and benzidine is not used any more (it is a banned substance according to Directive 88/364/EEC with respect to production and use). Exposure to benzidine can still occur due to release of benzidine as a decomposition product of dyes.

4.3. BIS(CHLOROMETHYL)ETHER (*CAS No.542-88-1; EC No.208-832-8*)

Current classification: Carc. Cat 1: R45, T+: R26, T: R24, R10, Xn: R22
Acute toxicity: Very toxic
T25: 0.0065 mg/kg/day (high potency)

4.3.1. Properties

Bis(chloromethyl)ether is a flammable liquid, b.p. 105°C. Soluble in alcohol and ether.

4.3.2. Carcinogenicity

After long-time exposure, it is carcinogenic to rats and mice by inhalation, producing malignant nasal and lung tumours. Topical application produced local carcinomas to mice. It is mutagenic to bacteria and induces DNA damage in cultured human lymphocytes. There are strong indications that it induces lung cancer in humans. No information is available on effects to animals or man after short-time exposure, or environmental fate (except for solubility data above).

4.3.3. Industrial use

It is widely used as a chloromethylating agent, particularly in the preparation of anion exchange resins and water repellents. Can be produced in runaway reactions. It is a contaminant (1-7%) of chloromethyl methyl ether.

4.4. CHLOROMETHYL METHYL ETHER (*CAS No: 107-30-2; EC No: 203-480-1*)

Current classification: Carc. Cat 1: R45, F: R11, Xn: R20/21/22
Acute toxicity: Harmful
T25: 0.5 mg/kg/day (TDx)

4.4.1. Properties

Chloromethyl methyl ether is a colourless flammable liquid, b.p. 59°C. Soluble in alcohol, ether, acetone and chloroform. Decomposes in water. Reported as biodegradable.

4.4.2. Carcinogenicity

After long-time exposure, this substance (technical grade) may cause pulmonary and nasal cancer in rats and hamsters. It produced local sarcomas after subcutaneous injection in mice and was an initiator for mouse skin tumours. It is mutagenic to bacteria. In cultured cell assay systems it induced DNA damage and cell transformations. Occupational exposure to the technical grade is causally associated with an increased risk of respiratory cancer, mainly lung cancer. As the technical grade is contaminated with bis(chloromethyl)ether, it is not possible to say if the effects are due to chloromethyl methyl ether itself, to the contaminant or to the combination. No information is available on effects to animals or man after short-time exposure.

4.4.3. Industrial use

It is widely used as a chloromethylation agent. The technical grade, which is the one used in industry, contains 1-7% bis(chloromethyl)ether.

4.5. DIMETHYLCARBAMOYL CHLORIDE (*CAS No: 79-44-7; EC No: 201-208-6*)

Current classification: Carc. Cat 2: R45, T: R23, Xn: R22, Xi: R36/37/38
Acute toxicity: Toxic
T25: 0.19 mg/kg/day (high potency)

4.5.1. Properties

Dimethylcarbamoyl chloride is a liquid, b.p. 165-167°C. It is rapidly hydrolysed.

4.5.2. Carcinogenicity

After long time exposure, it is carcinogenic in rats and hamsters after inhalation, producing malignant tumours of the nasal cavity. Subcutaneous, intraperitoneal and skin exposures in mice induce malignant tumours at the site of treatment. It is DNA damaging and mutagenic to bacteria. In cultured mammalian cells it is mutagenic, clastogenic and induces sisterchromatin exchanges. In in vivo assay systems micronuclei were increased. There are no adequate epidemiological data to assess the carcinogenicity to humans. No information is available on effects to animals or man after short-time exposure, or environmental fate.

4.5.3. Industrial use

It is used as a highly reactive alkylating agent in the production of drugs and pesticides.

4.6. DIMETHYL NITROSAMINE (*CAS No: 62-75-9; EC No: 200-549-8*)

Current classification: Carc. Cat 2: R45, T+: R26, T: R25-48/25, N:R51-53
Acute toxicity: Very toxic
T25: 0.34 mg/kg/day (high potency)

4.6.1. Properties

Dimethyl nitrosamine is a yellow liquid, b.p. 154°C. It is soluble in water, alcohol and ether.

4.6.2. Carcinogenicity

It is carcinogenic in many mammalian species after e.g. inhalation and ingestion, producing malignant tumours at various sites. In one study, tumours in the kidney and lung in mice were induced after administration of dimethyl nitrosamine in the drinking water (50mg/l) for one week. It is DNA damaging and mutagenic to bacteria and in cultured mammalian cells (where it also is cell transforming). In in vivo assay systems it is DNA damaging, clastogenic and it increases the frequencies of sister chromatic exchanges and micronuclei. Reported to be teratogenic in rats after single exposure. No adequate epidemiological data to assess the carcinogenicity to humans are available. No information is available on environmental fate.

4.6.3. Industrial use

It has been used in the production of liquid rocket fuel. Nowadays it is only used for research in mutagenicity and carcinogenicity. Exposure may for instance occur in environments where N-nitrosodimethylamine precursors, such as dimethylamine, come into contact with nitrosating agents such as nitrogen dioxide.

4.7. HEXAMETHYLPHOSPHORIC TRIAMIDE (*CAS No: 680-31-9; EC No: 211-653-8*)

Current classification: Carc. Cat 2: R45, Muta. Cat. 2: R46
Acute toxicity: -
T25: 0.02 mg/kg/day (high potency)

4.7.1. Properties

Hexamethylphosphoric triamide is a water-white liquid, b.p. 230-232°C, soluble in water and polar and non-polar solvents.

4.7.2. Carcinogenicity

After long-time exposure, it is carcinogenic in rats after inhalation, producing malignant tumours of the nasal cavity with a dose response relationship. It is not generally active in standard tests for DNA damage or mutations in bacteria. In cultured mammalian cells it is DNA damaging, mutagenic, clastogenic, increases sister chromatic exchanges and induces cell transformations. In in vivo assay systems micronuclei were increased and a dominant lethal test on mouse was positive. There are no epidemiological data to assess the carcinogenicity to humans. No information available on the effects to animals or man after short-time exposure, or environmental fate.

4.7.3. Industrial use

It is used as a solvent for polymers, as a selective solvent for gases, as a polymerisation catalyst and as a stabiliser against thermal degradation in polystyrene.

4.8. 2-NAPHTYLAMINE (*CAS No: 91-59-8; EC No: 202-080-4*) and/or salts

Current classification: Carc. Cat 1: R45, Xn: R22, N: R51-53
Acute toxicity: Harmful
T25: 40 mg/kg/day (TDx)

4.8.1. Properties

2-Naphtylamine is a white to faint pink solid (lustrous leaflets), m.p. 112°C, b.p. 306°C. It is soluble in hot water, alcohol and ether.

4.8.2. Carcinogenicity

2-Naphtylamine is carcinogenic in mice, rats, hamsters, dogs and monkeys after oral administration, producing bladder tumours (and also liver tumours in mice). It is DNA damaging and mutagenic to bacteria. In cultured mammalian cells it is DNA damaging, clastogenic and increases sister chromatic exchanges. In in vivo assay systems the mouse coat spot test was positive and it induced mutations in Drosophila melangogaster, but it did not increase sister chromatic exchanges. Epidemiological data show that it induces bladder cancer in humans. There is no doubt that 2-naphthylamine is a human bladder carcinogen. There is no reason to believe that the salts of 2-naphtylamine will act differently since they are rapidly dissociated in the gastrointestinal tract. No information available on the effects to animals or man after short-time exposure, or environmental fate (except for solubility data above).

4.8.3. Industrial use

2-Naphtylamine was used as an intermediate in the production of dyes, but is no longer used. It may not be used in concentrations equal to or greater than 0.1% by weight in substances and preparations placed on the market. It is formed in the pyrolysis of nitrogen-containing organic matter (e.g. L-glutamic acid and L-leucine at 700°C).

This compound is banned according to Directive 88/364/EEC with respect to production and use. The only exceptions, i.e. for scientific research and production as intermediate in closed systems, are not relevant from a practical point of view. The respective azo dyes which had been produced from these compounds in earlier times are not introduced or relevant in the EU anymore.

4.9. 1,3-PROPANESULTONE (*CAS No: 1120-71-4; EC No: 214-317-9*)

Current classification: Carc. Cat 2: R45, Xn: R21/22
Acute toxicity: Harmful
T25: 1.6 mg/kg/day

4.9.1. Properties

1,3-propanesultone is a white crystalline compound which melts at 31°C (b.p. 155-157°C) with a foul odour. It is soluble in chloroform.

4.9.2. Carcinogenicity

1,3-propanesultone is carcinogenic in rats after long-time oral administration and after one single intravenous injection, producing malignant tumours at various sites, including the brain. It is carcinogenic in the offspring of pregnant rats following one single prenatal intravenous injection, producing neurogenic tumours. Malignant skin tumours were developed in mice after a single application. It is DNA damaging and mutagenic to bacteria. In cultured mammalian cells it is DNA damaging, clastogenic and cell transforming. There are no data available to assess the carcinogenicity to humans. No information available on environmental fate.

4.9.3. Industrial use

1,3-Propanesultone is an alkylating agent. It is used as a chemical intermediate to introduce sulphopropyl groups into industrial products such as detergents, wetting agents, cation exchange resins and the modified starches used in the textile industry.

4.10. 4-NITRODIPHENYL (4-nitrobiphenyl) (*CAS No: 92-93-3; EC No: 202-204-7*)

Current classification: Carc. Cat 2: R45, N: R51-53
Acute toxicity: -
T25: DC (few data)

4.10.1. Properties

4-nitrobiphenyl is a light-yellow to reddish solid, m.p. 114°C, b.p. 340°C. It is insoluble in water, slightly soluble in cold alcohol and very soluble in ether.

4.10.2. Carcinogenicity

There is inadequate evidence for the carcinogenicity to animals. In one long-time exposure test on 4 dogs (with no controls), bladder carcinomas were induced in 3 of them. Two other experiments in dogs were negative, but total dosages were low. It is DNA damaging and mutagenic to bacteria and cultured mammalian cells, and in the latter it also induced cell transformations. There are no epidemiological data available to assess the carcinogenicity to humans. It is possible that 4-nitrobiphenyl is carcinogenic by virtue of its (proposed) metabolic conversion to 4-aminobiphenyl. No information available on the effects to animals or man after short-time exposure, or environmental fate (except for solubility data above).

4.10.3. Industrial use

4-nitrobiphenyl was used as a chemical intermediate in the preparation of 4-aminobiphenyl, but is no longer used (banned according to Directive 88/364/EEC with respect to production and use).

5. FINAL LIST OF SUBSTANCES PROPOSED

Proposal:

The Group propose the following substances to be included in the list of 'carcinogens' in Annex I Part 1 of the Seveso II Directive:

- **Acrylamide**
- **1,2-Dibromo-3-chloropropane**
- **1,2-Dimethylhydrazine**
- **Dimethyl sulphate**
- **Diethyl sulphate**
- **Benzotrichloride**
- **Hydrazine**
- **1,2-Dibromoethane**
- **The list of substances already named in Annex I Part 1 as 'carcinogens'**

6. INVESTIGATIONS ON QUALIFYING QUANTITIES

Having determined the substances to be included, the group discussed at length what qualifying quantities should be applied. It was decided that it was not possible to determine threshold levels on purely scientific grounds and that a pragmatic approach was the most reasonable option. The group studied a proposal by Prof. Sanner, which suggested that the principle of "equivalence of harm" would lead to qualifying quantities similar to those of the generic Annex I Part 2 "very toxic" category. However, taking into account public concern associated with carcinogens and the "precautionary principle" in the absence of full scientific data, it was decided to set the qualifying quantities one order of magnitude lower than those of "very toxic" substances. Thus the qualifying quantities for the named carcinogenic substances should be 0.5 tonnes for the application of Article6/7 and 2 tonnes for the application of Article9.

These qualifying quantities were also considered in relation to the ones set for TCDD, i.e. 1 kg, and it was concluded that the relationship is reasonable. When considering the qualifying quantities set in the Directive for the existing named carcinogens, the group noted that - unlike TCDD - the named substances did not appear to present and greater hazard than the new substances proposed, and that therefore the same qualifying quantities would be appropriate.

Proposal:

The Group propose the following qualifying quantities:

- **For application of Article6/7 : 0.5 tonnes (500 kg)**
- **For application of Article9 : 2 tonnes (2000 kg)**

It was also proposed that these qualifying quantities should apply whether dealing with the pure substance or a preparation in which the substance is present.

7. POINTS OF DISCUSSION AND OUTSTANDING POINTS OF CONCERN

A point of discussion in the group was whether to include polycyclic aromatic hydrocarbons (such as Benzo(a)pyrene) in the list or not. These substances are found as impurities in small quantities in oils and tars, especially coal tar. However, they are not used in industry as such. While some of them are quite potent carcinogens, they are typically found in such small quantities that in the event of, for example, a coal tar fire, their carcinogenic effect would not be a dominant concern. Their physical properties do not permit a wide dispersion of the substance in the case of an accident. Moreover, there are immense practical difficulties in knowing how much of each of these substances is present at an establishment. Benzo(a)pyrene, which is typical of this category, has been classified in the 24th ATP as dangerous for the environment (R50/53), and thus comes under other Seveso II Directive thresholds. On this grounds the group decided to exclude polycyclic aromatic hydrocarbons.

The group noted two outstanding points of concern associated with substances which could be generated in the course of an accident. One is that certain substances which may be carcinogenic have not received an EU classification because they are not deliberately made in or imported into the EU. The second is that certain known "dioxin precursors", in particular polychlorophenols and chlorphenoxic herbicides, could generate dioxins.

The proposal presented here does not address either of these points, but the group felt they should be noted for further consideration.

8. CONCLUSIONS

The group propose the following amendment to Directive 96/82/EC (Seveso II):

The list in Annex I Part 1 starting with "The following CARCINOGENS" should be extended to include, in addition to the substances currently named:

Acrylamide
1,2-Dibromo-3-chloropropane
1,2-Dimethylhydrazine
Dimethyl sulphate
Diethyl sulphate
Benzotrichloride
Hydrazine
1,2-Dibromoethane

and the corresponding qualifying quantities in Column 2 and Column 3 should be set at 0.5 tonnes and 2 tonnes respectively.