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Concise International Chemical Assessment Document 36

METHYL CYANOACRYLATE AND ETHYL CYANOACRYLATE

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The **International Programme on Chemical Safety (IPCS)**, established in 1980, is a joint venture of the United Nations Environment Programme (UNEP), the International Labour Organization (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.

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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 Organization (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.

International Chemical Safety Cards on the relevant chemical(s) are attached at the end of the CICAD, to provide the reader with concise information on the protection of human health and on emergency action. They are produced in a separate peer-reviewed procedure at IPCS. They may be complemented by information from IPCS Poison Information Monographs (PIM), similarly produced separately from the CICAD process.

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 170¹ 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

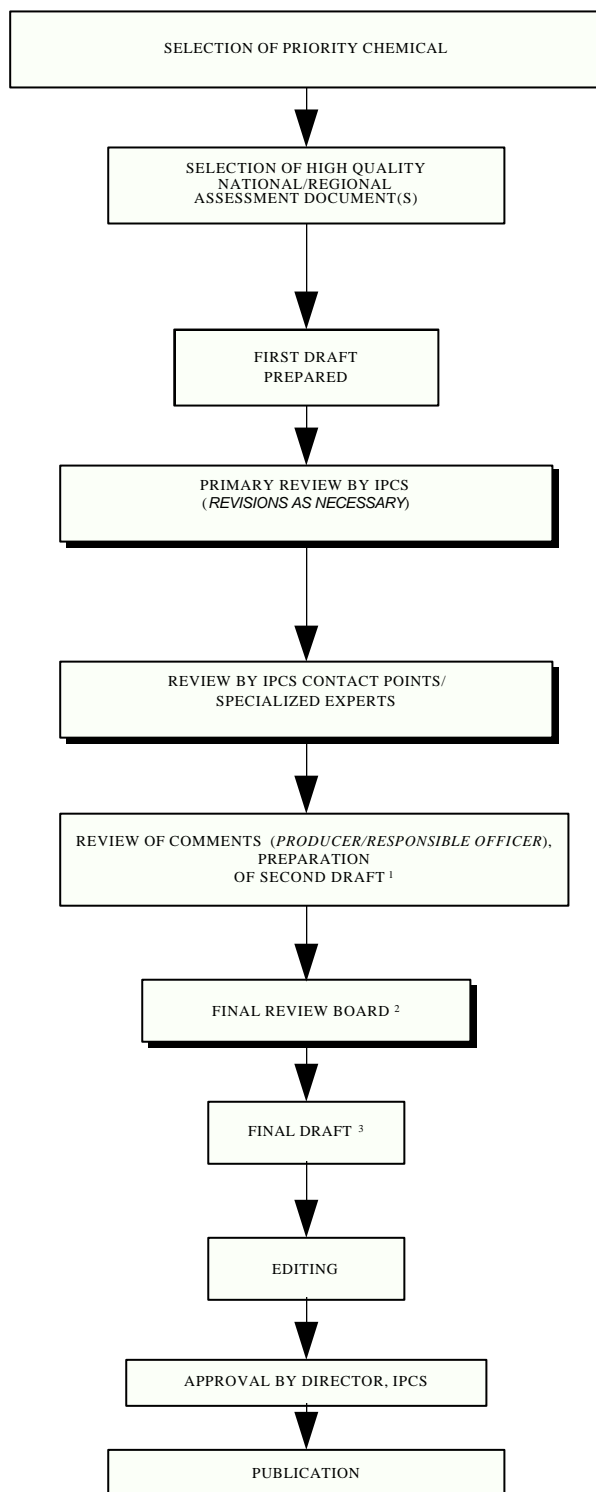
The flow chart on page 2 shows the procedures followed to produce a CICAD. These procedures are designed to take advantage of the expertise that exists around the world — expertise that is required to produce the high-quality evaluations of toxicological, exposure, and other data that are necessary for assessing risks to human health and/or the environment. The IPCS Risk Assessment Steering Group advises the Co-ordinator, IPCS, on the selection of chemicals for an IPCS risk assessment, the appropriate form of the document (i.e., EHC or CICAD), and which institution bears the responsibility of the document production, as well as on the type and extent of the international peer review.

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

The draft is then sent to an 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.

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.

A consultative group may be necessary to advise on specific issues in the risk assessment document.

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 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 methyl cyanoacrylate and ethyl cyanoacrylate was based on a review of human health concerns (primarily occupational) prepared by the United Kingdom's Health and Safety Executive (HSE) (Cary et al., 2000). Hence, this document focuses on exposures via routes relevant to occupational settings. Data identified as of September 1999 were covered. A further literature search was performed up to February 2000 to identify any extra information published since this review was completed. Since no source document was available for environmental fate and effects, the primary literature was searched by Dr Stuart Dobson, Centre for Environment and Hydrology, Monks Wood, United Kingdom; no environmental information was identified. 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 Geneva, Switzerland, on 8–12 January 2001. Participants at the Final Review Board meeting are listed in Appendix 3. The International Chemical Safety Cards for methyl cyanoacrylate (ICSC 1272) and ethyl cyanoacrylate (ICSC 1358), produced by the International Programme on Chemical Safety (IPCS, 1993a,b), have also been reproduced in this document.

Limited information, notably information that was quantitative with respect to exposure, was retrieved on the health effects of these cyanoacrylates. Also, the mode of action of cyanoacrylates for the key end-point, bronchoconstriction, after inhalation exposure could not be determined. As a result, the hazard and risk characterizations presented in this document are more limited than those in many previous CICADs. However, because of the widespread and uncontrolled exposure of the general public, it was considered important to produce this CICAD, to indicate the large data gaps and uncertainties in the present hazard and risk characterizations.

Methyl cyanoacrylate (MCA; CAS No. 137-05-3) and ethyl cyanoacrylate (ECA; CAS No. 7085-85-0) are clear, colourless liquids that react readily with water to form solid polymers.

The main applications for cyanoacrylates are as adhesives domestically and in a wide range of industrial environments — e.g., the manufacture of lampshades, plastics, electronics, scientific instruments, loudspeakers, shoes, jewellery, and sports equipment, and in cable joining, manicuring, dentistry, surgery, and mortuaries. Fingerprint development for police crime scene investigation can also use the properties of cyanoacrylates.

Airborne measurement of cyanoacrylates has proved problematic, particularly in industrial settings, where there may be interference due to the presence of formaldehyde, a common industrial contaminant. A measurement technique that is currently being validated has been developed by the Health and Safety Laboratory of the Health and Safety Executive in the United Kingdom.

As measured using this unvalidated technique, personal exposure during manufacture and use of ECA in the United Kingdom ranged from <0.005 to 0.41 ppm (<0.03–2.1 mg/m³), with 95% of the samples less than 0.19 ppm (0.97 mg/m³). MCA was in use in only one of the premises visited, and personal exposures were below the limit of detection in all samples (<0.01 ppm [<0.05 mg/m³]). Because of the ubiquitous nature of MCA/ECA adhesives throughout industry, it is not possible to estimate accurately the numbers of workers potentially exposed, but they are expected to run into the thousands.

There is potential for dermal exposure during the manufacture and use of MCA/ECA. No measured skin exposure data have been identified; however, low exposures would be anticipated. The possibility of bonding the skin to the contaminated surface means that, in practice, people tend to take great care when working with the substances.

From the data available, the key toxicological features of MCA and ECA seem to be as a result of local activity at the site of contact. Human data indicate that liquid MCA and ECA are not skin irritants as a result of single exposure. However, there are indications from human studies that repeated exposure can result in skin irritant effects. Eye irritancy has been observed in humans exposed to liquid cyanoacrylate adhesives.

No conclusions can be drawn with respect to the skin sensitization potential of MCA; the only study available did not provide any meaningful information. For ECA, there are a number of reports, but in only two individuals are the data consistent with a skin sensitization response. It should be borne in mind that there are likely to be considerable difficulties in performing tests on a substance that polymerizes rapidly on the skin; although speculative, it seems plausible that the removal of hardened adhesive could contribute to some of the skin reactions observed.

The main health effects that have been observed to date in relation to occupational exposure to MCA and ECA are eye and respiratory tract irritation. A number of studies, both case reports and workplace surveys, have

been reported in which occurrences of asthma have also been linked to exposure to ECA and/or MCA. The available information does not allow conclusions to be drawn regarding whether asthma was induced by an allergenic or an irritation mechanism. In many of the bronchial challenge tests, it seems that the challenge concentrations involved were directly irritant.

In a human experimental study using MCA vapour, no sensory irritant effects were reported at 1 ppm (4.5 mg/m³) (a human no-observed-adverse-effect level [NOAEL]); throat and nose "irritation" were subjectively reported from 2 to 20 ppm (9.1 to 91 mg/m³) or more. Eye irritation and "burning" were reported from 4 to 15 ppm (18 to 68 mg/m³) or more. At concentrations above 20 ppm (91 mg/m³), lacrimation and rhinorrhoea were reported (except in one individual for whom rhinorrhoea was reported at around 7 ppm [32 mg/m³]), and these were more pronounced at 50–60 ppm (227–272 mg/m³) (a level at which burning pain in the eyes was also reported). In the absence of similar quantitative data for ECA, it would seem reasonable to assume that a similar dose–response relationship exists for ECA as for MCA, given their close structural similarities, similar physicochemical properties, and, for most end-points, similar toxicological profiles.

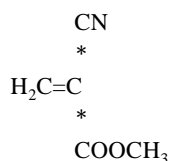
There are limited exposure data available, especially for non-occupational settings. Also, owing to the limited toxicological database, it is difficult to make definitive comments about the potential risks to human health.

2. IDENTITY AND PHYSICAL/CHEMICAL PROPERTIES

2.1 Methyl 2-cyanoacrylate

MCA (C₅H₅NO₂, CAS No. 137-05-3) is a clear, colourless liquid with a strong, acrid odour. It reacts readily with water to form a solid polymer. The substance is soluble or partially soluble in methyl ethyl ketone, toluene, *N,N*-dimethylformamide, acetone, and nitromethane (Cary et al., 2000).

Some of the more commonly used synonyms for MCA include methyl cyanoacrylate, 2-propenoic acid 2-cyanomethyl ester, and methyl " -cyanoacrylate. The structural formula for MCA is shown below:

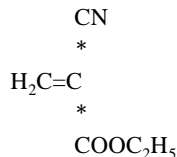


Additional physical/chemical properties for MCA are presented in Table 1 and in the International Chemical Safety Card reproduced in this document.

2.2 Ethyl 2-cyanoacrylate

ECA (C₆H₇NO₂, CAS No. 7085-85-0) is a clear, colourless liquid with a strong, acrid odour. It reacts readily with water to form a solid polymer. It is soluble in methyl ethyl ketone, toluene, acetone, *N,N*-dimethylformamide, and nitromethane. Contact with alcohols, amines, or water may cause polymerization. Degradation products include formaldehyde. Thermal decomposition products may include hydrogen cyanide and oxides of carbon and nitrogen (Cary et al., 2000).

Some of the more commonly used synonyms for ECA include ethyl cyanoacrylate and 2-propenoic acid 2-cyanoethyl ester. The structural formula for ECA is given below:



Additional physical/chemical properties for ECA are presented in Table 1 and in the International Chemical Safety Card reproduced in this document.

3. ANALYTICAL METHODS

3.1 Environmental monitoring

There are no data available on methods for the analysis of MCA or ECA in water or any other environmental media.

3.2 Workplace air monitoring

A number of measurement systems have been employed, although there are technical difficulties and inaccuracies with many of them.

One method involves collecting airborne cyanoacrylate using a bubbler containing dilute sodium

Table 1: Some physical/chemical properties of methyl cyanoacrylate and ethyl cyanoacrylate.^a

Property	Methyl cyanoacrylate	Ethyl cyanoacrylate
Boiling point	48–49 °C at 0.33–0.36 kPa	54–56 °C at 0.21–0.40 kPa
Vapour pressure	<0.27 kPa at 25 °C	<0.27 kPa at 25 °C
Saturated vapour concentration	<2700 ppm (<12 260 mg/m ³) at 25 °C (calculated)	<2700 ppm (<13 770 mg/m ³) at 25 °C (calculated)
Conversion factor	1 ppm = 4.6 mg/m ³ at 20 °C, 101.3 kPa	1 ppm = 5.2 mg/m ³ at 20 °C, 101.3 kPa

^a From Cary et al. (2000).

hydroxide (Walker & Guiver, 1981). The cyanoacrylate in the resulting solution is then degraded to produce formaldehyde, which is then derivatized and measured spectrophotometrically. This method is not applicable to personal monitoring due to the impinger sampling system and is subject to interference, since formaldehyde is present in many workplace atmospheres. Many of the existing exposure and toxicology data have been generated using this measurement system. In view of the disadvantages discussed here, particularly the potential for interference from formaldehyde, the validity of such data must be questioned.

Method No. 55 of the US Occupational Safety and Health Administration involves sampling onto a sorbent tube containing phosphoric acid-coated XAD-7 (OSHA, 1985). The tube is subsequently solvent desorbed, and the resulting solution is analysed by high-pressure liquid chromatography (HPLC). However, in laboratory trials, this method was found to give false, low results. The HPLC analysis procedure was shown to work well; therefore, the fault must lie with the sampling device.

Another method involves sampling onto Tenax followed by solvent desorption and analysis by gas chromatography (Gaid & Jedrzejczak, 1989). However, for satisfactory operation of the method, a thermionic-specific detector must be coupled to the gas chromatograph. This type of detector can suffer from poor repeatability.

A method for measuring airborne cyanoacrylates, recently developed and currently being validated by the Health and Safety Laboratory of the Health and Safety Executive, uses various parts of previously published techniques (Keen & Pengelly, 1996). Airborne cyanoacrylates are collected onto a Tenax sorbent tube (as in the Gaid & Jedrzejczak [1989] method), which is subsequently solvent desorbed. The resulting solution is analysed by HPLC, using the analytical conditions described in OSHA Method No. 55. The method may be applied to short-term (15-min) or long-term (2- to 4-h) sampling. The Tenax sorbent tube may not be used for sampling periods of greater than 4 h. Cyanoacrylates

may also be sampled into an impinger containing 0.2% phosphoric acid in acetonitrile, although this method is not applicable to personal monitoring. Both techniques may be applied to MCA and ECA. As the system is not yet fully validated, detection limits are not clearly defined.

3.3 Biological monitoring in humans

There are no published methods for the biological monitoring of humans occupationally exposed to MCA or ECA.

4. SOURCES OF HUMAN AND ENVIRONMENTAL EXPOSURE

There is extensive use of ECA- and MCA-based adhesives, not only in a very wide range of industrial applications, but also as household products. Presumably, there is a potential for spillage onto the skin and exposure via inhalation, particularly as most people would not use personal protective equipment. Owing to the nature of the source document of this CICAD (Cary et al., 2000), this section focuses mainly on the occupational rather than domestic applications of MCA and ECA.

4.1 Manufacture

One method of production of ECA involves condensing an alkyl cyanoacetate with formaldehyde in the presence of a base catalyst to yield a low molecular weight cyanoacrylic ester polymer. Depolymerization at high temperature gives the 2-cyanoacrylic ester. Cyanoacrylates have many applications as the unmodified monomer, but they are usually formulated with additives, such as inhibitors, thickeners, plasticizers, and colorants, to improve their function as adhesives.

4.2 Use

Industrial applications of cyanoacrylate glues are widespread and diverse, many of them being small-scale uses. However, the main industrial applications for cyanoacrylates as adhesives include the manufacture of lampshades, plastics, electronics, scientific instruments, loudspeakers, shoes, jewellery, and sports equipment, and in cable joining, manicuring (attaching false nails, repairing cracks), dentistry, surgery, and mortuaries. Fingerprint development for police crime scene investigation can also use the properties of cyanoacrylates.

It is not possible to quantify precisely the amount of MCA or ECA used in industry because of the difficulty in differentiating between minor industrial use and domestic use. There is the added complication of out-working, such as in jewellery manufacture. However, industrial usage in the United Kingdom is likely to be of the order of 200 tonnes/year.

5. ENVIRONMENTAL TRANSPORT, DISTRIBUTION, AND TRANSFORMATION

There are no data available on the transport, distribution, or transformation of MCA or ECA in the environment.

6. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

6.1 Environmental levels

There are no data available on levels of MCA or ECA in environmental media.

6.2 Occupational exposure

The sample analysis procedures used prior to 1997 were discovered to be unreliable due mainly to polymerization onto sample detectors and/or interference with formaldehyde (Keen & Pengelly, 1996). The Health and Safety Laboratory therefore developed a reliable method that is currently being validated and commissioned a survey of exposure within the United Kingdom for a cross-section of occupational environments (see Cary et al., 2000).

The sole manufacturer of ECA in the United Kingdom produces several hundred tonnes annually. During this production, about 14 people are potentially

exposed. Personal exposures during manufacture have been measured up to 0.21 ppm (1.1 mg/m³) for short-term (40-min) activities and an 8-h time-weighted average (TWA) exposure of 0.06 ppm (0.31 mg/m³). MCA is not manufactured in the United Kingdom. Cyanoacrylates are imported in the form of glues. Repackagers fill 3-g tubes or 10- or 25-ml bottles from larger bulk containers (20-kg or 55-litre drums). Exposure to ECA is typically up to 0.1 ppm (0.51 mg/m³) for repackaging tasks. During repackaging, approximately 50 people are potentially exposed to ECA or MCA.

During use as an adhesive, personal exposure to ECA ranged from <0.005 to 0.41 ppm [<0.03 to 2.1 mg/m³], with 95% of the samples less than 0.19 ppm (0.97 mg/m³). MCA was in use in only one of the premises visited (a speaker manufacturer) during the Health and Safety Executive survey, and personal exposures for this were below the limit of detection in all samples (<0.01 ppm [<0.05 mg/m³]). Because of the ubiquitous nature of MCA/ECA adhesives throughout industry, it is not possible to estimate accurately the numbers of workers potentially exposed, but they are expected to run into the thousands.

MCA and ECA are also used for the visualization of fingerprints for criminal investigations. Exhibits are exposed to ECA vapour inside a sealed cabinet, which allows development of the fingerprints by selectively bonding with polymerized ECA. Short-term (11-min) exposures of up to 0.05 ppm (0.26 mg/m³) were measured, although the 8-h TWA exposure for the operator was less than 0.01 ppm (0.05 mg/m³). Approximately 140 workers are potentially exposed in this sector.

There is potential for dermal exposure during the manufacture of MCA/ECA due to splashes and contact with contaminated surfaces. No measured skin exposure data have been identified; however, the rapid polymerization of thin films of MCA/ECA would mean that the monomer would be available for contact for a short time only. This, and the small application rate (drops) or the use of an activator, would indicate low exposures. In addition, the immediate consequences of dermal contact with MCA/ECA — bonding the skin to the contaminated surface — mean that, in practice, people tend to take great care when working with the substances. The use of suitable gloves will reduce exposure significantly; however, gloves are unlikely to be worn in some situations where MCA/ECA adhesives are used because of the need for manual dexterity.

7. COMPARATIVE KINETICS AND METABOLISM IN LABORATORY ANIMALS AND HUMANS

No information is available relating to inhalation exposure to MCA.

Following oral administration of 0.05 ml liquid ^{14}C -MCA (as monomer and polymer) to groups of two rats, radioactivity was detected in the urine, indicating that some absorption had occurred (Ousterhout et al., 1969). For the rats receiving liquid MCA monomer into the oral cavity by syringe, approximately 2% of the radiolabel administered was recovered in urine over 48 h. For rats receiving poly-MCA directly into the stomach, the total mean recovery from urine samples after 4 days was approximately 16%. A mean total of 18% of the radiolabel administered was recovered from faeces on completion of the 4-day sampling period. However, the detection of radiolabel in the stool samples may well reflect the passage of poly-MCA particles directly through the gastrointestinal tract rather than any absorption and metabolism.

Following dermal application of 0.5 ml liquid ^{14}C -MCA to groups of two rats, radioactivity was detected in the urine, indicating limited dermal absorption (up to 4% of the applied dose over a 6-day collection period) (Ousterhout et al., 1968). When the liquid was applied to skin with the epidermis removed, the amount of radiolabel recovered from urine increased approximately 3-fold.

No information on the metabolism of MCA is available.

No toxicokinetic information is available on ECA.

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

8.1 Single exposure

8.1.1 Inhalation

Groups of five male and five female rats were exposed for 1 h to 21 000 mg/m³ of ECA aerosol (droplet size not stated), resulting in 70% mortality during the first 4 days post-exposure (Wo & Shapiro, 1982). Macroscopic pathological examination of the seven decedents revealed pulmonary and intestinal haemorrhage in all animals and splenic haemorrhage in six of seven animals.

8.1.2 Oral

No mortalities were observed following the administration of 5000 mg/kg body weight of liquid MCA by oral gavage to a group of six male rats (Bach & Fogleman, 1974a). Pilo-erection and lethargy were observed in all animals until day 6 post-administration. The extent of the macroscopic pathological examination was unclear, but a large hardened mass filled the entire stomach of each animal; this was almost certainly solidified adhesive. Extended caeca were also reported.

One mortality occurred in a group of six male rats receiving a single oral gavage dose of 5000 mg/kg body weight of liquid ECA with a 14-day observation period, but there were no other clinical signs of toxicity (Suppers & Fogleman, 1973). The extent of the macroscopic pathological examination was again unclear, as was the incidence of findings. The stomach was reported to contain a solidified mass; this was again likely to be polymerized adhesive.

8.1.3 Dermal

There are no data on dermal exposure to MCA.

Liquid ECA (2000 mg/kg body weight, approximately 100% purity) was applied under a semi-occlusive dressing to a group of rabbits (unknown number) for a 24-h period (Bach & Fogleman, 1973). No mortalities and no signs of systemic toxicity were reported over a 14-day observation period.

8.2 Irritation and sensitization

8.2.1 Respiratory tract irritation

The single inhalation exposure study available (see section 8.1) indicates that MCA and ECA have the potential to be respiratory tract irritants in animals.

8.2.2 Skin irritation

Liquid MCA (0.5 ml, approximately 100% purity) was applied under a semi-occlusive dressing to each of six rabbits for a 24-h period (Bach & Fogleman, 1974b). Slight erythema (a mean score of 0.75 over 72 h according to the European Union [EU] system) was seen, but there were no signs of oedema.

Similarly, liquid ECA was applied to each of six rabbits for a 24-h period (Deprospro & Fogleman, 1973a). Slight erythema and slight oedema were observed; for both of these observations, the mean score (EU system) was 0.83.

8.2.3 Eye irritation

One drop (~0.1 ml) of liquid MCA (approximately 100% purity) was applied to one eye of each of three New Zealand White rabbits (Bach & Fogleman, 1974c). For three other rabbits, the eyes were washed (presumably with saline or water) shortly after instillation.

At 24 h, observations could be performed only on two rabbits whose eyes were unwashed because of adhesion problems. At all other time points, all three rabbits were available for observation. White discharges were observed during the study. For conjunctival reactions, the mean score (EU system) for redness was 1.75. For chemosis, the mean value was 0.5; corneal opacity, 0.75; and iridial reactions, 0.5. All reactions decreased in intensity during the observation period, and no abnormalities were seen after 7 days. Reactions were exacerbated by washing immediately after application, presumably due to rapid polymerization enhanced by the presence of water or saline (scores were not presented for these animals).

Similar results were seen in an earlier study also using liquid MCA instilled into the eyes of rabbits (Bloomfield et al., 1963).

In a study involving liquid ECA (approximately 100% purity), one drop (~0.1 ml) was applied to one eye of each of nine New Zealand White rabbits (Deprospo & Fogleman, 1973b). Discharge (undefined) was observed at all time points during the 72-h observation period. For conjunctival reactions, the mean score (EU system) for redness was 1.37. For chemosis, the mean value was 0.96; corneal opacity, 1.0; and iridial reactions, 0.48. All reactions decreased in intensity during the 72-h observation period.

8.2.4 Sensitization

An unstated number of guinea-pigs received four injections of 0.2% MCA in ethanol/saline solution with Freund's complete adjuvant into the footpad and into the nape of the neck on day 0 (Parker & Turk, 1983). On day 7, the maximum non-irritant concentration (not stated) was applied to the shaved flank. The same concentration was applied topically at different sites on the flank once a week for up to 12 weeks. There was no mention of the use of control animals. MCA did not appear to produce positive skin reactions.

There are no data on the skin sensitization potential of ECA in animals.

There are no animal data on the respiratory sensitization potential of MCA or ECA.

8.3 Short-term and medium-term exposure

There are no reliable data available for the effects of MCA or ECA following short-term or medium-term exposure by the inhalation, oral or dermal route.

8.4 Long-term exposure and carcinogenicity

There are no data available from long-term toxicity/carcinogenicity studies on MCA or ECA.

8.5 Genotoxicity and related end-points

8.5.1 *In vitro* studies in prokaryocytes

The following studies in *Salmonella typhimurium* provide the only *in vitro* data available for MCA and ECA. Liquid MCA and ECA (>98% purity) were tested for mutagenic potential in *S. typhimurium* strains TA 98, TA 100, TA 1535, TA 1537, and TA 1538 with and without metabolic activation (Rietveld et al., 1987). The concentration range tested was 0–4000 µg/plate. MCA was toxic to the bacteria at 500 µg/plate or more, and ECA was toxic at concentrations greater than 2000 µg/plate. A positive result was obtained with TA 100 only for MCA in the presence and absence of metabolic activation. A negative result was obtained for ECA in all the strains tested.

In the same study, a spot test for the potential mutagenicity of volatile compounds was carried out on *S. typhimurium* TA 100 with and without metabolic activation. An inhibition zone (with no colonies) was seen around the adhesive drop for each of three MCA-based adhesives with and without metabolic activation. Within the background lawn, there was an accumulation of small, revertant colonies adjacent to the inhibition zone. This was indicative of a mutagenic effect. No mutagenic effect was seen for the ECA-based adhesive.

A similar set of studies and results (positive for MCA, negative for ECA) was obtained in *S. typhimurium* TA 100, with and without metabolic activation (Andersen et al., 1982).

8.5.2 *In vitro* studies in mammalian cells

There are no data available.

8.5.3 *In vivo* studies in non-mammalian eukaryotes

In a standard Basc test, male *Drosophila melanogaster* were incubated with 0, 0.03, 0.045, or 0.06 ml liquid MCA adhesive (Farrow et al., 1984). In positive and

negative controls, the incidence of recessive lethal mutations upon mating was 13.6% and 0.1%, respectively. For MCA adhesive-exposed male flies, an incidence of 0.05–0.07% recessive lethal mutations was seen following mating, indicating a negative result for MCA in this system.

8.5.4 *In vivo studies in mammalian cells*

In an *in vivo* mouse micronucleus study, groups of five male and five female mice received a single intraperitoneal injection of 600 mg/kg body weight of an MCA-based adhesive (approximately 99% MCA) as a suspension in mineral oil (San Sebastian, 1988). In a preliminary range-finding assay, mortalities were observed at 750 mg/kg body weight or more.

In the main study, five males and five females were sacrificed at 30, 48, and 72 h, and bone marrow samples were obtained for analysis of micronuclei. All animals showed clinical signs of systemic toxicity (e.g., decreased activity, decreased body tone). There were no statistically significant increases in the number of micronucleated polychromatic erythrocytes in any of the MCA-treated groups at any sacrifice time. A significant decrease in the ratio of polychromatic to normochromatic erythrocytes (P/N ratio) was observed at 48 h among mice receiving the test material. In summary, in a well-conducted micronucleus assay producing signs of bone marrow toxicity and other clinical signs of toxicity, MCA produced no evidence of mutagenicity.

There are no other *in vivo* data for MCA, and there is no information on the effects of ECA in mammalian cells.

8.6 Reproductive toxicity

There are no data available on the effects of MCA or ECA on fertility or development.

9. EFFECTS ON HUMANS

Cyanoacrylate adhesives contain up to 10% stabilizers, plasticizers, or thickeners (such as an acrylate or methacrylate). Most of the commercially available adhesives are likely to be based on ECA and to a lesser extent MCA, although other cyanoacrylates have been marketed (such as isobutyl cyanoacrylate, 2-cyano-butylacrylate, amyl- and heptyl cyanoacrylate, or other complex alkyl cyanoacrylates). This should be borne in mind when considering studies in which the composition of the adhesive is poorly described. In addition, the

removal of hardened polymerized adhesive from the skin is likely to cause sloughing and irritation of the skin.

9.1 Chamber studies

There is one briefly reported experimental study available in which odour perception and sensory irritation were investigated in humans exposed to MCA vapour (McGee et al., 1968). The study involved the use of an exposure chamber; however, due to the difficulties in generating MCA exposure atmospheres, exposure was achieved via a simulated work procedure in which the subjects applied the adhesive to microscope slides or other glass sheets. No ventilation of the chamber was provided in order to allow the build-up of vapour concentrations. Concentrations of MCA were controlled to a degree by the method, amount, or speed of application, and the operations were graduated so as to produce vapour concentrations ranging from 1 to 60 ppm (4.5 to 272 mg/m³). Air samples were taken in the breathing zone of each individual with sampling periods of 5 min, and collection was repeated 10 times/h for the duration of the study. The sampling involved drawing air through a sodium hydroxide solution in a bubbler, and the analytical procedures were described in detail in the published paper; these appeared to have adequate sensitivity and reliability and would not have suffered from interference due to the presence of other industrial contaminants. Subjects filled in a questionnaire at the end of each 5-min sampling period to indicate odour perception and irritancy responses.

In preliminary trials in which an unstated number of subjects spread the adhesive over a large area (38 cm²), marked eye and nose irritation were reported at 40–60 ppm (182–272 mg/m³). For two individuals, blurred vision was reported some time after the exposure and persisted for approximately 2 h.

Fourteen individuals participated in the main study, with some performing the simulated occupational tasks more than once; adhesives were applied dropwise onto glass slides using a syringe or directly from the adhesive container. These procedures are a closer simulation of many of the occupational uses of the cyanoacrylate adhesives than was the preliminary study.

From a graphical summary of the irritancy responses, no effects were reported in any of the 14 subjects at 1 ppm (4.5 mg/m³). The odour threshold was reported to be 1–5 ppm (4.5–23 mg/m³). Throat and nose “irritation” were subjectively reported from 2 to 20 ppm (9.1–91 mg/m³) or more, although the severity was unclear (at 2 ppm [9.1 mg/m³], it can be seen from the graph that no more than 3 of the 14 people reported effects). Eye irritation and “burning” were reported from 4 to 15 ppm (18 to 68 mg/m³) or more, although from the

graph it is impossible to tell exactly what proportion of volunteers reported effects. At concentrations above 20 ppm (91 mg/m³), lacrimation and rhinorrhoea were reported (except for one individual in whom rhinorrhoea was reported at around 7 ppm [32 mg/m³]), and these were more pronounced at 50–60 ppm (227–272 mg/m³) (a level at which painful eye irritation was also reported).

The study report suffers from a number of limitations. A lack of detail was provided on the total duration and numbers of exposures, although, on the basis of sampling times given, exposures at each concentration would seem to have been at least 5 min and possibly up to 1 h. There was no indication of the nature of the questionnaire provided, and no control subjects were used. The effects detailed were self-reported, and many would be subjective (except obvious signs of irritation such as lacrimation). Despite these limitations, it is possible to identify a NOAEL for irritancy due to MCA vapour of 1 ppm (4.5 mg/m³) from this study. At around 2 ppm (9.1 mg/m³), the nasal and throat effects were of unclear severity in no more than 3 of the 14 volunteers, with marked effects (rhinorrhoea and lacrimation) at around 20 ppm (91 mg/m³) or more.

9.2 Case reports

9.2.1 Skin effects

A recent case report describes an individual who showed a skin reaction associated with occupational exposure to an ECA-based adhesive (90% ECA), initially on the backs of hands but later progressing to all of the hands, lower arms, and abdomen (Bruze et al., 1995). The only positive skin reaction in a patch testing series was to ECA. Negative reactions were reported for a group of 20 control subjects patch-tested with 100% adhesive. Overall, this study demonstrates that this individual showed a skin sensitization reaction towards ECA.

Another case report details an individual with peri-orbital eczema, marked oedema of the eyelids, erythematous and scaly lips, and dry eczema of the fingertips in association with occupational exposure to two different ECA-based adhesives (Tomb et al., 1993). In a series of patch tests, the only skin reactions that were observed occurred following exposure to ECA. These results demonstrate a sensitization rather than an irritant reaction to ECA for this individual. In addition, the authors noted that an initial occupationally related skin reaction on the fingers was only slight, compared with the more severe reaction on the eyelids. This may have been due to rubbing the eyelids with the fingers.

Another brief report (Belsito, 1987) describes three cases of skin reactions in connection with occupational exposure to an ECA-based adhesive (approximately

100% ECA). The skin reactions were present on the hands of all three individuals and additionally around the eyelids of one person. In a series of patch tests, all three individuals were positive towards the dried adhesive. For two of the subjects, positive reactions to the entire “standard” range cast doubt on the specificity of skin reactions in relation to ECA, and the positive responses reported by all three subjects to dried adhesive would also seem to be unusual. It is difficult to be sure, therefore, whether or not these represent reliable cases of skin sensitization.

No firm conclusions can be drawn regarding the skin sensitization potential of ECA or MCA from the case-studies reported by Fitzgerald et al. (1995) and Jacobs & Rycroft (1995). It was noted that these individuals had a history of atopic dermatitis or eczema prior to occupational exposure to cyanoacrylate-based adhesives or showed positive responses to a number of substances in the patch tests.

Another brief report describes five further cases of skin reactions, including reactions on the face and eyes, in connection with occupational exposure to cyanoacrylate adhesives (Calnan, 1979). However, the process at work also involved the use of a soldering iron and consequently exposure to solder fume. The absence of positive results in patch tests and the occasional association of skin responses with soldering operations suggest that the effects were not due to the cyanoacrylate adhesive (studies indicating skin irritation or skin sensitization reactions to solder flux fume are summarized in a recent review by Smith et al. [1997]).

Following the observation of extensive and persistent skin reactions on the chest, scapulae, abdomen, and thighs and a scaly, mild pruritis in an individual, positive results to patch tests were observed with dried adhesive and to another ECA-based adhesive (Shelley & Shelley, 1984). However, it is doubtful that this represents a case of skin sensitization, as reactions were not observed at the main site of contact, the hands. Furthermore, a positive reaction to a hardened adhesive is unexpected, and the results of the skin biopsy could be suggestive of an infection that would not be related to the use of an adhesive.

Three cases of self-adhesion of the digits due to accidental spillage of liquid cyanoacrylate-based adhesives were reported by Maitra (1984). There were no apparent signs of skin irritation.

9.2.2 Ocular effects

The report by Maitra (1984) also described a case of accidental spillage of liquid cyanoacrylate adhesive in one eye. The subject reported lacrimation, pain in the

eye, and blurred vision. Twenty-four hours after treatment (non-surgical), the glue had disappeared, although there was some residual, but undefined, defect of the corneal epithelium. One week later, the cornea was completely healed, and visual acuity was fully restored.

Similar ocular effects were reported in a study by Campbell (1983), in which adhesion in one eye resulted in lacrimation and corneal abrasion. Treatment was non-surgical, and a full recovery was reported after 3 days.

In addition, Dean & Krenzelok (1989) reported 34 cases of accidental ocular exposure to cyanoacrylate-based adhesives, none of which resulted in permanent injury.

9.2.3 Respiratory tract effects

It should be noted that for many studies on MCA/ECA, there was no clear indication of whether or not bronchial challenge tests had been performed in a blinded manner — i.e., whether subjects or investigators were aware of which substances were used at challenge. It is recognized that blinding to the substance used at challenge may significantly affect the outcome of the test and hence the overall interpretation of results (an example of the significance of this was reported by Stenton et al. [1994] in their investigations of glutaraldehyde).

Unless otherwise stated, none of the subjects described in these studies was reported to have asthma prior to exposure to the adhesive. In many cases, there are difficulties in interpreting the results of the studies, as control subjects were often not used for these bronchial challenge tests, and there was no clear indication of whether or not the exposure concentrations involved would have caused irritation among “normal” people. For some reports, there is uncertainty about whether or not the adhesive induced the state of asthma, particularly when reactions appeared to develop 2–4 weeks after starting work with the adhesive, as this seems a rather short time period for asthma induction (examples of a broad range and number of substances indicating latency for asthma induction in the order of several months to years are summarized in a review of potential asthmagens by HSE [1998]).

A case report describes an individual with work-related respiratory tract symptoms that were first reported 4 months after initial exposure to an ECA-based adhesive (Nakazawa, 1990). Two bronchial challenge tests were conducted. In addition, a “healthy” individual was challenged under similar conditions, and no signs of bronchial hyperresponsivity or other “clinical” signs were noted. The results demonstrated an immediate (second challenge) and a delayed asthmatic response

(first challenge). The lack of response in the healthy individual would suggest that the challenge concentration was not irritating to normal airways. There is uncertainty about whether or not ECA induced the asthmatic state, although the latency of respiratory problems is suggestive of specificity.

In another case report, an individual reported various respiratory tract signs and symptoms associated with the use of an ECA-based adhesive for making model aeroplanes (Kopp et al., 1985). Bronchial challenge tests were conducted using cyanoacrylate and a non-cyanoacrylate adhesive. The non-cyanoacrylate bronchial challenge was reported to be negative, as was an initial challenge test of 15-min duration. However, in a test with longer exposure, a significant decrease in forced expiratory volume in 1 s (FEV_1) was recorded with the concurrent observation of cough and chest tightness. Six months after continued avoidance of ECA-based adhesives, respiratory symptoms had disappeared, and challenge testing with methacholine did not show any signs of bronchial hyperresponsiveness. Overall, this individual appeared to show a delayed asthmatic response towards the ECA-based adhesive. The absence of a reaction to methacholine some months after avoidance of the adhesive suggests that the use of ECA was responsible for the bronchial hyperresponsiveness.

Four further cases of asthma in connection with individuals exposed to ECA and one case related to exposure to MCA have been reported (Lozewicz et al., 1985). Bronchial challenge tests indicated evidence of asthmatic responses following exposure specifically to MCA or ECA. In at least four of the five cases, there was a significant fall in FEV_1 . For one of the five, the nature of the adhesive used at bronchial challenge was not clearly indicated, and the response was weaker. No controls were used, and there was no clear indication of whether or not exposures would have been irritant to “normal” people. In addition, the cases observed here reported asthmatic responses very soon after initial exposure to the cyanoacrylate adhesive.

Over a 6.5-year period, 12 cases of asthmatic responses associated with occupational exposure to cyanoacrylate-based adhesives were identified from 880 hospital admissions (Savonius et al., 1993). The actual cyanoacrylates involved were not known, and the range of industries from which cases were drawn was quite diverse. The times from first exposure to the onset of symptoms varied considerably, between 1 week and approximately 14 years.

Each individual was bronchially challenged by simulation of occupational conditions (and also with a placebo test). Tests were performed “blind,” although in

some instances (it was not clear which) the individuals could identify the substance by smell. Challenge with a cyanoacrylate (in most cases unspecified) under simulated occupational conditions resulted in maximum reductions in peak expiratory flow (PEF), which ranged from 19% in one individual up to 64% in another. Also, it should be noted that PEF is not an ideal diagnostic; it is a less stringent parameter than FEV₁ and subject to greater variance. No testing was carried out in control subjects, and it was unclear whether the responses elicited represented irritant reactions. There were no tests for non-specific bronchial hyperresponsivity. Skin prick tests were performed using a “cyanoacrylate”–human serum albumin (HSA) conjugate, and no skin responses were seen. However, it is unclear whether or not the “cyanoacrylate”–HSA conjugate was an appropriate antigenic material.

For two individuals, there was no decrease in PEF, and reactions were identified as immediate rhinitis and immediate pharyngolaryngitis, which would suggest irritant rather than delayed asthmatic responses. Responses were described as “late” or “dual” for the other 10 individuals.

Although some of the cases appear to represent asthmatic responses, no firm conclusions can be drawn on the possible asthmagenic potential of ECA/MCA from this report. This is because the exact nature of the cyanoacrylates was not defined, the concentrations involved in the bronchial challenge tests were not measured, and it is unclear whether or not they were above the threshold for irritancy. There was no test for non-specific bronchial hyperresponsiveness in the subjects with an agent such as methacholine or histamine, and there were no “control” subjects involved. Also, it is not known whether the previous exposures encountered in the workplace would have been irritant.

Another case report details an individual claiming work-related skin irritation (face only) and exhibiting eye irritation, dry cough, and wheezing in connection with exposure to an ECA-based adhesive (De Zotti & Larese, 1990). The skin irritation was a subjective self-reported symptom, there being no visible signs of abnormality. Bronchial challenge produced reductions in FEV₁ ranging from 12 to 24%, but there were also subjective symptoms of skin irritation on the face, chest discomfort, dizziness, and scotoma (impaired vision). Furthermore, there were observable body tremors and changes in an electrocardiograph (ECG) pattern. In summary, this individual appeared to be showing a variety of adverse responses following exposure to an ECA-based adhesive, including a decrease in FEV₁. However, there was no control subject against which to compare the response, and the subjective nature of some of the symptoms in the light of no objective changes makes

interpretation more difficult. The changes in ECG may be suggestive of some other underlying health problem. Overall, it is felt that this does not represent a convincing case of asthma in relation to cyanoacrylate exposure.

Three cases of possible asthma and rhinitis associated with occupational exposure to ECA-based adhesives were reported by Roy et al. (1989). Changes in FEV₁ were reported for only one person — being reduced to 54% of the expected value while at work, and recovering to 83% of the expected value after a 1-month period away from work. For the two other people, no bronchial challenge was conducted, and the respiratory symptoms reported (cough and chest tightness) were complicated by smoking and the observation of symptoms occurring without exposure to the ECA-based adhesive. Due to the limited extent of investigations in this report, no conclusions on the asthmagenic potential of ECA can be drawn.

Another study detailed the case reports of four individuals reputedly showing signs of occupational asthma due to exposure to cyanoacrylate-based adhesives, although spray painting was also involved in the process (Poppius et al., 1986). The initial respiratory effects were observed very soon after initial exposure to the adhesive (i.e., within 1 week), which may be more suggestive of an irritation response. In this study, the exact nature of the adhesives and the spray paint was not described, making results difficult to interpret. Assessment of responses in the bronchial challenge test was by PEF. Two individuals did not react to the “cyanoacrylate” in challenge tests. For the other two individuals, the challenge tests indicated asthma-like responses to the adhesives. The report also lacked critical detail regarding the conduct of investigations (such as histamine tests). Overall, there are too many uncertainties to draw firm conclusions from this report.

9.3 Epidemiological studies

Respiratory tract effects were studied in a group of 450 workers at a facility involved in monomer manufacture and repackaging of MCA- and ECA-based adhesives (Goodman et al., 2000). The group included all workers employed over a 17-year period, each of whom had routine annual or biennial health investigations, including pulmonary function tests. Job histories were reconstructed on the basis of company records, and workers were divided into cohorts based on cumulative exposure potential using current personal monitoring data. Historical personal monitoring results were not available, but the authors felt that as the technology used at this plant was essentially unchanged over the period of this study, then the exposure reconstruction was valid. The airborne measurement techniques used

were not available at the time of publication of this report; hence, the validity of values quoted is currently unclear. Personal monitoring indicated a maximum “short-term” (not further defined) airborne ECA concentration of 1.5 ppm [7.7 mg/m³] (geometric mean 0.2 ppm [1.0 mg/m³]). Values were not presented for exposure to MCA, presumably because the measurement technique cannot distinguish between the two substances.

Obstructive pulmonary disease was implicated by an FEV₁/forced vital capacity (FVC) ratio of less than 0.7. Further cases for consideration included workers with physician-diagnosed rhinitis, sinusitis, or conjunctivitis. Cohort analyses were expressed as relative risk ratios comparing “cyanoacrylate-exposed workers” (divided into low-, medium-, and high-exposure categories) with “unexposed controls” (administrative staff working at the same factory) and had been adjusted for age, sex, smoking status, time of follow-up, and “survival.” Case-control analyses were also performed using the groups of workers who were “suspected” to have pulmonary obstruction and those reporting symptoms of rhinitis, sinusitis, or conjunctivitis. Odds ratios (OR) for pulmonary effects were calculated for cases that had been exposed to cyanoacrylates and cases in the control group.

In the cohort analysis, workers exposed to cyanoacrylates did not show an increased risk of pulmonary obstruction compared with unexposed workers based on pulmonary function tests (hazards ratio 0.66, 95% confidence interval [CI] 0.29–1.5). In the case-control analysis, the OR for “suspected” cases of pulmonary obstruction in workers ever exposed to cyanoacrylates (adjusted for confounding factors) was 0.99 (95% CI 0.57–1.75). For those exposed to peak exposures (up to 1.5 ppm [7.7 mg/m³]), the OR was 0.53 (95% CI 0.17–1.48). Workers who had reported at least one episode of rhinitis, sinusitis, or conjunctivitis were more likely to have been exposed to cyanoacrylates (OR 1.61, 95% CI 0.82–3.29). For peak exposures, high cumulative exposure was more strongly associated with these symptoms (OR 1.93, 95% CI 0.74–4.98).

The authors also noted that the medical records reported only two cases of asthma over 17 years, and one of those was in a worker not exposed to cyanoacrylates.

Overall, there was no increased risk of pulmonary obstruction associated with cyanoacrylate exposure in this study. However, there was an association with ocular and nasal irritation, particularly with peak exposures.

The prevalence of eye and respiratory tract symptoms in a group of 73 workers in a factory using an ECA-based adhesive was examined using a questionnaire (London & Lee, 1986). Following the questionnaire survey, pre- and post-shift spirometry and frequent PEF measurements were conducted on 23 individuals who reported some respiratory effects and on a group of 20 who did not. Twenty-one of these 73 workers used the adhesive at least once per week. All of these 21 were among the 43 individuals participating in spirometry and PEF tests. No bronchial challenge testing was conducted in this study.

It was not clear how long workers had been employed in this factory. Work station measurements indicated that the mean ECA exposure level was less than 0.35 ppm (1.8 mg/m³) (7-h TWA). However, as indicated in section 6.2, little credence can be attached to the values quoted, as the method has not been validated.

The questionnaire showed increases in the prevalence of some subjectively recorded symptoms relating to the respiratory tract of workers exposed to the ECA-based adhesive — e.g., wheezing or whistling breath, episodes of shortness of breath, and chest tightness. ECA-exposed workers also reported a significantly higher prevalence of symptoms of nasal irritation and a higher prevalence of symptoms of eye irritation.

For spirometry results, five people showed a 5% difference in pre- and post-shift FEV₁ values, although, on the basis of clinical history and the spirometry, only three of these five could be considered as possibly having occupational asthma. Ten other individuals identified by the physicians from clinical history as possibly having occupational asthma did not show even a 5% decrease in FEV₁ values.

Eleven individuals showed a 20% variability in PEF measurements. Of the 13 people identified from clinical history and FEV₁ values as potentially having occupational asthma, only 5 showed a 20% or more variability in PEF values. Two out of the remaining 30 who did not have any significant clinical history or changes in FEV₁ also had a significant (>20%) variability in PEF. Hence, due to these inconsistencies, the PEF data were of questionable value in detecting asthma.

Objective assessments revealed no confirmed cases of asthma in this population. However, the questionnaire indicated that the ECA-based adhesive was associated with eye and respiratory tract irritation, although these effects were not correlated with reliable personal exposure levels.

The prevalence of eye and respiratory tract symptoms in a group of 16 workers occupationally exposed to an ECA-based adhesive in the manufacture of car components was examined using a questionnaire (Lee & London, 1985). The adhesive was described as 84% ECA; the other components of this adhesive were not listed. The mean ECA level was measured using the colorimetric technique of McGee et al. (1968), which is subject to interference from formaldehyde. Hence, as formaldehyde is a common airborne contaminant in the workplace, the reliability of the exposure data quoted in this report is uncertain. A group of five lead-exposed workers employed at this factory was used as the control group for this study.

The prevalence of “stuffed nose” and “irritated or sore throat” was statistically significantly higher in the adhesive-exposed workers when compared with lead-exposed workers at this factory. In addition, “bloody nose” was reported in 9 of 16 ECA-exposed workers compared with 1 of 5 lead-exposed workers. There were increases in some other subjective symptoms recorded among the adhesive-exposed workers compared with the lead-exposed controls, which were considered of doubtful toxicological importance. Also, the processes at this factory generated a “large amount” of soldering fume, which was not adequately ventilated and is likely to have confounded some of the irritant effects seen.

The value of the study is limited by the small group sizes and the high prevalence of the subjectively reported symptoms of eye and respiratory tract irritation among the adhesive-exposed and the “control” group. Overall, no clear conclusions can be drawn in relation to the health effects of ECA.

Respiratory symptoms in 253 forensic workers were studied using a questionnaire, and results were compared with those of 202 control subjects (Trottier et al., 1994). The results of the questionnaire revealed increases in some subjectively reported respiratory symptoms, particularly cough, among forensic workers compared with controls. There was also a slight increase in the reporting of wheezing among the forensic workers. Overall, it is impossible to draw any conclusions from this study about the health effects of MCA or ECA, as occupational exposure was likely to have involved many other substances, and no bronchial challenge tests were conducted on the forensic workers to investigate respiratory effects.

The poor descriptions of effects and exposure conditions and the absence of a control group make the study of a group of 12 workers by Lenzi et al. (1974) of limited value. However, it does indicate the potential for eye and respiratory tract irritation following exposure to airborne MCA. This study also included X-ray examina-

tion, haematology, urinalysis, and “clinical” and dermatological examination; there were no significant adverse effects on these clinical parameters.

10. EFFECTS ON OTHER ORGANISMS IN THE LABORATORY AND FIELD

There are no data available on the effects of MCA or ECA on other organisms in the laboratory and field.

11. EFFECTS EVALUATION

11.1 Evaluation of health effects

11.1.1 *Hazard identification and dose–response assessment*

No toxicokinetic information is available for ECA. The only information available for MCA is from studies in rats exposed via the oral and dermal routes; no information is available relating to inhalation exposure. Following oral administration of radiolabelled MCA (as monomer and polymer), radioactivity was detected in the urine, indicating that some (up to about 16%) absorption had occurred. Following dermal application of radiolabelled MCA, radioactivity was detected in the urine of rats, indicating limited dermal absorption (up to 4% of the applied dose over a 6-day collection period). When radiolabelled MCA was applied to skin with the epidermis removed, the amount of radiolabel recovered from urine increased approximately 3-fold. No information on metabolism is available.

ECA is of moderate acute toxicity following single inhalation exposure in animals. Seventy per cent mortality resulted from a 1-h exposure to 21 000 mg/m³ ECA aerosol. MCA and ECA are of low single-dose toxicity (LD₅₀ > 5000 mg/kg body weight) to animals by the oral route. ECA is also of low single-dose toxicity (LD₅₀ > 2000 mg/kg body weight) by the dermal route. Although there is no experimental information available, on the basis of the similar chemical structures and similar results obtained for most toxicological end-points, MCA would also be expected to be of low single-dose toxicity by the inhalation and dermal routes.

Animal data indicate that ECA and MCA vapour and aerosols are eye and respiratory tract irritants. Eye irritancy has been observed in animals exposed to liquid MCA and ECA. Animal data indicate that liquid MCA and ECA are not skin irritants as a result of single expo-

sure. The available animal studies on skin sensitization contain no data on ECA and no useful information on MCA.

There are no repeated-exposure studies on ECA and no reliable information relating to MCA.

Few studies have been conducted to investigate the mutagenic potential of MCA or ECA. The only *in vitro* studies available are from bacteria: MCA is a direct-acting mutagen in bacteria, specifically in a single *S. typhimurium* strain (TA 100). In contrast, ECA gives negative results in such bacterial cells. The reason for this difference in response is not clear. In an *in vivo* mouse bone marrow micronucleus test, MCA did not produce a significant increase in micronuclei when tested at a dose level producing signs of bone marrow and general toxicity. There are no other *in vivo* data for MCA, and there is no *in vivo* information available for ECA.

There are no useful carcinogenicity or reproductive toxicity data available.

Human data indicate that liquid MCA and ECA are not skin irritants as a result of single exposure. There are indications from human studies that repeated exposure can result in skin irritant effects. Eye irritancy has been observed in humans exposed to liquid cyanoacrylate adhesives.

In a human experimental study using MCA vapour, no sensory irritant effects were reported at 1 ppm (4.5 mg/m³); throat and nose "irritation" were subjectively reported from 2 to 20 ppm (9.1 to 91 mg/m³) or more. Eye irritation and "burning" were reported from 4 to 15 ppm (18 to 68 mg/m³) or more. At concentrations above 20 ppm (91 mg/m³), lacrimation and rhinorrhoea were reported (except for one individual in whom rhinorrhoea was reported at around 7 ppm [32 mg/m³]), and these were more pronounced at 50–60 ppm (227–272 mg/m³) (a level at which burning pain in the eyes was also reported). There is no similar information on ECA, but a similar profile of responses would be expected.

There is extensive use of ECA- and MCA-based adhesives, not only in a very wide range of industrial applications, but also as household products. Presumably, there is a potential for a substantial number of people to be exposed by spillage onto the skin and for inhalation exposure, particularly as most consumers would not use any personal protective equipment. There is limited evidence for skin sensitization with MCA; the only study available did not provide any meaningful information. For ECA, there are a number of case reports suggesting problems, but for only two individuals are the data consistent with a skin sensitization response. It

should be borne in mind that there are likely to be considerable difficulties in performing standard tests on substances that polymerize rapidly on the skin, and, although speculative, it seems plausible that removal of hardened adhesive could contribute to some of the skin reactions observed.

A number of studies, both case reports and workplace surveys, have been reported in which occurrences of asthma have been linked with exposure to ECA and/or MCA. In many bronchial challenge tests, it seems that the challenge concentrations involved were directly irritant. Hence, it cannot be judged whether the mechanism of the observed bronchoconstrictive effects is allergic or irritative; in many cases, the responses seen can be attributed to irritant effects exacerbating a pre-existing asthmatic condition (or one induced by some agent other than MCA/ECA).

11.1.2 Criteria for setting tolerable intakes/ concentrations or guidance values for methyl cyanoacrylate and ethyl cyanoacrylate

Overall, the toxicological database for MCA and ECA is poor, and it is questionable whether a meaningful risk assessment can be conducted, particularly with regard to the implications for human health for such end-points as carcinogenicity, genotoxicity, and reproductive toxicity.

A major cause for concern with respect to MCA and ECA has been the issue of occupational asthma. However, given the extremely widespread exposure to ECA and MCA and the absence of case reports on asthma among consumers, it can be concluded that these substances have at most a limited potency for inducing asthma. Hence, the main health effects that can be observed in the short term in relation to occupational exposure to MCA and ECA are eye and respiratory tract irritation, for which a NOAEL has been identified in a human volunteer study using MCA at around 1 ppm (4.5 mg/m³) (5-min exposures). At 2 ppm (9.1 mg/m³) and above, poorly characterized symptoms of irritancy have been reported. In the absence of quantitative data for ECA, it would seem reasonable to assume that a similar dose–response relationship exists for ECA as for MCA, given their close structural similarities, similar physicochemical properties, and, for most end-points, similar toxicological profiles.

11.1.3 Considerations for follow-up

In order to arrive at a meaningful risk assessment for methyl and ethyl cyanoacrylate, it would be useful to obtain further information on the following aspects.

There are very limited data in relation to the toxicokinetics of MCA and ECA; little is known about absorption (particularly by the inhalation route, which is of prime importance in occupational settings), metabolism, or distribution. Such data would prove useful in determining the toxicological profiles. Rapid polymerization may limit absorption by any route, although the validity of this assertion is uncertain.

The available toxicological information is limited, with no meaningful data on genotoxicity or on repeated exposure (including carcinogenicity and reproductive toxicity). There is also no clear understanding of the mechanism(s) of the bronchoconstriction reactions.

For many of the studies, particularly those not conducted within a laboratory, the weaknesses of the assessment of the exposure make dose–response assessments very uncertain.

11.2 Evaluation of environmental effects

There are no relevant data available with which to evaluate the environmental effects of MCA or ECA.

12. PREVIOUS EVALUATIONS BY INTERNATIONAL BODIES

Previous evaluations by other international bodies were not identified.

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APPENDIX 1 — SOURCE DOCUMENT

Cary R, Evans P, Cocker J, Keen C, Dyne D (2000) *Methyl cyanoacrylate and ethyl cyanoacrylate risk assessment document EH72/13*. Sudbury, Suffolk, HSE Books (ISBN 0 7176 1843 9)

The authors' draft version was initially reviewed internally by a group of approximately 10 HSE experts, mainly toxicologists but also involving 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 comprises 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)
Mr R. Chapman (Chemical Industries Association)
Dr H. Cross (Trades Union Congress)
Mr D. Farrer (Independent Consultant)
Dr A. Fletcher (Trades Union Congress)
Dr I.G. Guest (Chemical Industries Association)
Dr A. Hay (Trades Union Congress)
Dr L. Levy (Institute of Occupational Health, Birmingham)
Dr T. Mallet (Chemical Industries Association)
Mr A. Moses (Independent Consultant)
Dr R. Owen (Trades Union Congress)
Mr J. Sanderson (Independent Consultant)
Dr A. Spurgeon (Institute of Occupational Health, Birmingham)

APPENDIX 2 — CICAD PEER REVIEW

The draft CICAD on cyanoacrylates 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:

A. Aitio, International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland

M. Baril, International Programme on Chemical Safety/ Institut de Recherche en Santé et en Sécurité du Travail du Québec, Montreal, Quebec, Canada

S. Batt, National Industrial Chemicals Notification and Assessment Scheme, Australia

R. Benson, Drinking Water Program, US Environmental Protection Agency, Denver, CO, USA

J. Caldwell, National Center for Environmental Assessment, US Environmental Protection Agency, Research Triangle Park, NC, USA

R. Chhabra, National Institute of Environmental Health Sciences, National Institutes of Health, Research Triangle Park, NC, USA

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C. Hiremath, National Center for Environmental Assessment, US Environmental Protection Agency, Research Triangle Park, NC, USA

J. Montelius, National Institute for Working Life, Stockholm, Sweden

K. Ziegler-Skylakakis, Commission of the European Communities/European Union

APPENDIX 3 — CICAD FINAL REVIEW BOARD

Geneva, Switzerland, 8–12 January 2001

Members

Dr A.E. Ahmed, Molecular Toxicology Laboratory, Department of Pathology, University of Texas Medical Branch, Galveston, TX, USA

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Dr S. Czerczak, Department of Scientific Information, Nofer Institute of Occupational Medicine, Lodz, Poland

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Dr O.M. Faroon, Division of Toxicology, Agency for Toxic Substances and Disease Registry, Atlanta, GA, USA

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Dr A. Hirose, Division of Risk Assessment, National Institute of Health Sciences, Tokyo, Japan

Dr P.D. Howe, Centre for Ecology and Hydrology, Cambridgeshire, United Kingdom (*Rapporteur*)

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Dr P.G. Jenkins, International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland

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METHYL 2-CYANOACRYLATE

1272

October 2000

CAS No: 137-05-3
 RTECS No: AS7000000
 EC No: 607-235-00-3

2-Propenoic acid, 2-cyano-, methyl ester
 2-Cyanoacrylic acid methyl ester
 Mecrylate
 $C_5H_5NO_2 / CH_2=C(CN)COOCH_3$
 Molecular mass: 111.1

TYPES OF HAZARD/ EXPOSURE	ACUTE HAZARDS/SYMPTOMS	PREVENTION	FIRST AID/FIRE FIGHTING
FIRE	Combustible. Gives off irritating or toxic fumes (or gases) in a fire.	NO open flames.	Foam, powder, carbon dioxide. NO water.
EXPLOSION	Above 79°C explosive vapour/air mixtures may be formed.	Above 79°C use a closed system, ventilation.	In case of fire: cool drums, etc., by spraying with water but avoid contact of the substance with water.

EXPOSURE		AVOID ALL CONTACT!	IN ALL CASES CONSULT A DOCTOR!
Inhalation	Cough. Headache. Sore throat.	Ventilation, local exhaust, or breathing protection.	Fresh air, rest. Refer for medical attention.
Skin	Dry skin. Redness. Pain.	Protective gloves. Protective clothing.	Remove contaminated clothes. Rinse and then wash skin with water and soap. Refer for medical attention.
Eyes	Redness. Pain.	Face shield 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.	

SPILLAGE DISPOSAL	PACKAGING & LABELLING
Ventilation. Remove all ignition sources. Do NOT wash away into sewer. Absorb liquid in sand or inert absorbent. Let solidify. Use face shield. (Extra personal protection:) filter respirator for organic gases and vapours.	Xi Symbol R: 36/37/38 S: (2-)23-24/25-26

EMERGENCY RESPONSE	STORAGE
	Separated from incompatible materials, see Chemical Dangers. Well closed. Store only if stabilized.

IMPORTANT DATA

Physical State; Appearance

COLOURLESS LIQUID

Chemical dangers

The substance polymerizes rapidly, especially under the influence of moisture. The substance decomposes on heating or on burning producing toxic and irritating fumes/gases including nitrogen oxides.

Occupational exposure limits

TLV (as TWA): 0.2 ppm; (ACGIH 2000).

 MAK: 2 ppm; 8 mg/m³; (1999)

Routes of exposure

The substance can be absorbed into the body by inhalation of its vapour.

Inhalation risk

A harmful contamination of the air will be reached rather slowly on evaporation of this substance at 20°C.

Effects of short-term exposure

The vapour is irritating to the eyes and the respiratory tract. Inhalation of vapour may cause asthmatic reactions (see Notes). Immediately glues (sticks to) biological tissues.

Effects of long-term or repeated exposure

Repeated or prolonged contact with skin may cause dermatitis.

PHYSICAL PROPERTIES

Boiling point: 66°C

Melting point: -40°C

Relative density (water = 1): 1.1

Vapour pressure, Pa at 25°C: 24

Relative vapour density (air = 1): 3.8

Relative density of the vapour/air-mixture at 20°C (air = 1): 1

Flash point: 79°C

Octanol/water partition coefficient as log Pow: 0.03 (estimated)

ENVIRONMENTAL DATA

NOTES

Depending on the degree of exposure, periodic medical examination is indicated. 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. An added stabilizer or inhibitor can influence the toxicological properties of this substance, consult an expert.

ADDITIONAL INFORMATION

LEGAL NOTICE

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

ETHYL 2-CYANOACRYLATE**1358**

March 2001

CAS No: 7085-85-0
RTECS No: UD3330050
EC No: 607-236-00-9

2-Cyano-2-propenoic acid, ethyl ester
2-Cyanoacrylic acid, ethyl ester
Ethyl alpha-cyanoacrylate
C₈H₇NO₂
Molecular mass: 125

TYPES OF HAZARD/ EXPOSURE	ACUTE HAZARDS/SYMPTOMS	PREVENTION	FIRST AID/FIRE FIGHTING
FIRE	Combustible.	NO open flames.	In case of fire in the surroundings: all extinguishing agents allowed.
EXPLOSION	Above 75°C explosive vapour/air mixtures may be formed.	Above 75°C use a closed system, ventilation, and explosion-proof electrical equipment.	In case of fire: keep drums, etc., cool by spraying with water.

EXPOSURE			
Inhalation		Ventilation.	Fresh air, rest. Refer for medical attention.
Skin	Redness. Pain.	Protective gloves. Protective clothing.	Refer for medical attention.
Eyes	Redness. Pain.	Safety goggles.	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.	Refer for medical attention.

SPILLAGE DISPOSAL	PACKAGING & LABELLING
Ventilation. Collect leaking liquid in sealable containers. Absorb remaining liquid in sand or inert absorbent and remove to safe place.	Xi Symbol R: 36/37/38 S: (2-)23-24/25-26

EMERGENCY RESPONSE	STORAGE
	Cool.

IMPORTANT DATA

Physical State; Appearance

COLOURLESS LIQUID

Chemical dangers

The substance polymerizes rapidly. The substance decomposes on heating or on burning producing toxic and irritating fumes/gases including nitrogen oxides and cyanides.

Occupational exposure limits

TLV not established.

Routes of exposure

The substance can be absorbed into the body by inhalation of its vapour.

Inhalation risk

No indication can be given about the rate in which a harmful concentration in the air is reached on evaporation of this substance at 20°C.

Effects of short-term exposure

The substance irritates the eyes severely, and the skin.

Effects of long-term or repeated exposure

Repeated or prolonged contact may cause skin sensitization.

PHYSICAL PROPERTIES

Boiling point: 54-56°C

Flash point: 75°C c.c.

ENVIRONMENTAL DATA

NOTES

ADDITIONAL INFORMATION

LEGAL NOTICE

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

RÉSUMÉ D'ORIENTATION

Ce CICAD relatif au cyanoacrylate de méthyle (MCA) et au cyanoacrylate d'éthyle (ECA) est basé sur une mise au point rédigée par le *Health and Safety Executive* du Royaume-Uni (HSE) au sujet des effets de ces composés pourraient avoir sur la santé humaine, principalement en milieu professionnel (Cary et al., 2000). Ce document est donc principalement consacré aux voies d'exposition qui existent sur les lieux de travail. Les données prises en compte vont jusqu'en septembre 1999. Une recherche bibliographique complémentaire a été effectuée jusqu'à février 2000 afin de relever les données qui auraient pu être publiées depuis le premier dépouillement de la littérature. Etant donné l'absence de tout document sur le devenir de ces composés dans l'environnement et leurs effets à ce niveau, un dépouillement de la littérature originale a été effectué par Stuart Dobson, du *Centre for Environment and Hydrology*, Monks Wood, Royaume-Uni. Aucune donnée d'ordre écologique n'a pu être trouvée. On trouvera à l'appendice 1 des indications sur le mode d'examen par des pairs ainsi que sur les sources documentaires utilisées. 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 de la réunion du Comité d'évaluation finale qui s'est tenue à Genève (Suisse) du 8 au 12 janvier 2001. La liste des participants à cette réunion figure à l'appendice 3. Les fiches d'information internationales sur la sécurité chimique relatives au cyanoacrylate de méthyle (ICSC 1272) et au cyanoacrylate d'éthyle (ICSC 1358) établies par le Programme international sur la sécurité chimique (IPCS, 1993a,b) sont également reproduites dans le présent document.

On n'a obtenu que des informations limitées, s'agissant notamment de données quantitatives sur l'exposition, relatives aux effets sanitaires de ces cyanoacrylates. En particulier, il n'a pas été possible de déterminer le mécanisme d'action à la base de leur principal effet toxicologique après exposition par la voie respiratoire, à savoir une bronchoconstriction. Dans ces conditions, le danger et le risque que constituent ces composés ne sont pas aussi bien caractérisés que dans nombre de précédents CICAD. Toutefois, en raison de l'exposition généralisée et sans restrictions de la population générale à ces substances, on a jugé important de rédiger un CICAD, afin de mettre en lumière les grandes lacunes et incertitudes que comporte, à son stade actuel, la caractérisation du danger et du risque inhérents à ces produits.

Le cyanoacrylate de méthyle (MCA; N° CAS 137-05-3) et le cyanoacrylate d'éthyle (ECA; N° CAS 7085-85-0) sont des liquides limpides et incolores qui

réagissent facilement avec l'eau pour former des polymères solides.

La principale utilisation des cyanoacrylates consiste dans la fabrication de colles à usage domestique mais qui ont aussi des applications industrielles très variées, par exemple pour les abat-jour, les matières plastiques, l'électronique, les instruments scientifiques, les haut-parleurs, les chaussures, la joaillerie, les équipements sportifs, les connexions de câbles, la manucurie, l'art dentaire, la chirurgie et la thanatologie. On peut également utiliser certaines propriétés des cyanoacrylates pour la prise d'empreintes digitales sur les lieux d'un crime.

Le dosage des cyanoacrylates dans l'air pose des problèmes, notamment en milieu industriel, où la présence de formaldéhyde, un contaminant industriel courant, se révèle gênante. Une technique de dosage, actuellement en cours de validation, a été mise au point au Royaume-Uni, par le *Health and Safety Laboratory* du *Health and Safety Executive*.

En utilisant cette technique encore non validée, on a constaté qu'au Royaume-Uni, l'exposition individuelle au cours de la production et de l'utilisation de l'ECA allait de <0,005 à 0,41 ppm (<0,03-2,1 mg/m³), avec 95 % des échantillons qui se situaient à moins de 0,19 ppm (0,97 mg/m³). Le MCA n'était utilisé que dans un seul des lieux visités et l'exposition individuelle s'est révélée inférieure à la limite de détection pour tous les échantillons (<0,01 ppm [<0,05 mg/m³]). En raison du caractère ubiquiste des colles à base de MCA/ECA dans l'ensemble des industries, il n'est pas possible d'estimer le nombre de travailleurs exposés, mais on peut s'attendre à ce qu'ils soient plusieurs milliers.

Il y a possibilité d'exposition cutanée lors de la fabrication et de l'utilisation de ces produits. On n'a pas trouvé de données tirées de mesures d'exposition cutanée, mais on peut penser que cette exposition est faible. Le risque d'adhésion de la peau à la surface encollée fait que dans la pratique, les usagers font très attention lorsqu'ils utilisent ces produits.

D'après les données disponibles, les propriétés toxicologiques essentielles du MCA et de l'ECA résultent d'effets locaux au point de contact. Selon des données obtenues sur des sujets humains, ces deux composés ne provoquent pas d'irritation cutanée à l'état liquide lors d'une seule exposition. Toutefois, ces mêmes données indiquent qu'une exposition répétée peut avoir un effet irritant sur la peau. Une irritation de la muqueuse oculaire a été observée chez des sujets humains exposés à des colles cyanoacryliques liquides.

On ne peut tirer aucune conclusion concernant le pouvoir irritant du MCA; la seule étude dont on dispose ne fournit aucune information significative. Dans le cas de l'ECA, de nombreux rapports existent, mais les données ne sont révélatrices d'une sensibilisation cutanée que chez deux sujets seulement. Il ne faut pas perdre de vue la très grande difficulté qu'il y a à effectuer des tests avec des produits qui se polymérisent rapidement sur la peau; il semble plausible que l'irritation cutanée soit due en partie aux efforts pour gratter la colle durcie qui adhère à la peau, mais ce n'est là qu'une hypothèse.

Les principaux effets sanitaires observés jusqu'à présent par suite d'exposition professionnelle au MCA et à l'ECA consistent en une irritation des yeux et des voies respiratoires. Il existe un certain nombre d'études, consistant en analyse de rapports médicaux ou en enquêtes sur les lieux de travail, qui établissent un lien entre l'asthme et l'exposition au MCA ou à l'ECA. Les données disponibles ne permettent pas de décider si cet asthme a été provoqué par un allergène ou par une irritation. Dans nombre de tests de provocation bronchique, il semble que les concentrations utilisées avaient un effet irritant direct.

Lors d'une étude expérimentale sur sujets humains, on a constaté qu'à l'état gazeux, le MCA ne provoquait aucun effet irritant sensitif à la concentration de 1 ppm (4,5 mg/m³) (dose sans effet indésirable observable ou NOAEL); on a fait état d'une sensation subjective d'« irritation » de la gorge et du nez aux doses comprises entre 2 et 20 ppm (9,1 à 91 mg/m³) ou davantage. Les sujets ont ressenti une irritation oculaire et une sensation de « brûlure » entre 4 et 15 ppm (18 à 68 mg/m³) ou davantage. Aux concentrations supérieures à 20 ppm (91 mg/m³), les sujets se sont plaints d'effet lacrymogène et de rhinorrhée (sauf dans un cas où la rhinorrhée est apparue à partir de 7 ppm [32 mg/m³], ces effets étant plus prononcés aux doses de 50-60 ppm (227-272 mg/m³) (doses auxquelles les sujets ont également signalé une sensation de brûlure oculaire). En l'absence de données quantitatives similaires concernant l'ECA, il paraît raisonnable de supposer qu'il existe une relation dose-réponse analogue pour ce composé, étant donné sa grande similitude de structure et de propriétés physico-chimiques avec le MCA et le fait que pour la plupart des paramètres toxicologiques, il présente un profil analogue à celui du MCA.

Les données sur l'exposition sont limitées, notamment hors du lieu de travail. En outre, étant donné que la base de données toxicologique est restreinte, il est difficile de se prononcer de manière définitive sur le risque que ces produits représentent pour l'Homme.

RESUMEN DE ORIENTACIÓN

El presente CICAD sobre el cianoacrilato de metilo y el cianoacrilato de etilo se basó en un estudio de los problemas relativos a la salud humana (fundamentalmente de carácter ocupacional) preparado por la Dirección de Salud y Seguridad (HSE) del Reino Unido (Cary et al., 2000). Por consiguiente, este documento se concentra en las exposiciones por vías de importancia para el entorno ocupacional. Se incluyen los datos identificados hasta septiembre de 1999. Se realizó una nueva búsqueda bibliográfica hasta febrero de 2000 para localizar cualquier información adicional que se hubiera publicado desde que se completó esta revisión. Dado que no se disponía de documentos originales sobre el destino y los efectos en el medio ambiente, el Dr. Stuart Dobson, del Centro de Ecología e Hidrología de Monks Wood (Reino Unido), realizó una búsqueda en la bibliografía principal; no se encontró información relativa al medio ambiente. La información sobre el carácter del examen colegiado y la disponibilidad del documento original se presenta 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 Ginebra (Suiza) del 8 al 12 de enero de 2001. La lista de participantes en esta reunión figura en el apéndice 3. Las Fichas internacionales de seguridad química para el cianoacrilato de metilo (ICSC 1272) y el cianoacrilato de etilo (ICSC 1358), preparadas por el Programa Internacional de Seguridad de las Sustancias Químicas (IPCS, 1993a,b), también se reproducen en el presente documento.

Se encontró información limitada sobre los efectos en la salud de estos cianoacrilatos, en particular datos cuantitativos con respecto a la exposición. Asimismo, tras una exposición por inhalación no se pudo determinar el mecanismo de acción de los cianoacrilatos para el efecto final más importante, la broncoconstricción. En consecuencia, las caracterizaciones del peligro y el riesgo que se presentan en este documento son más limitadas que las expuestas en numerosos CICAD anteriores. Sin embargo, se considera importante la preparación de este CICAD, debido a la exposición generalizada y no controlada del público general, para indicar el gran número de lagunas e incertidumbres que existen en las presentes caracterizaciones del peligro y el riesgo.

El cianoacrilato de metilo (CAS N° 137-05-3) y el cianoacrilato de etilo (CAS N° 7085-85-0) son líquidos transparentes incoloros que reaccionan fácilmente con el agua para formar polímeros sólidos.

Las cianoacrilatos se utilizan sobre todo como adhesivos domésticos y en una gran variedad de industrias, por ejemplo la fabricación de pantallas de lámparas, plásticos, electrónica, instrumentos científicos, altavoces, calzado, joyería, equipo de deporte, empalmes de cables, manicura, odontología, cirugía y depósitos de cadáveres. Las propiedades de los cianoacrilatos se pueden aprovechar también en el descubrimiento de huellas dactilares durante la investigación policial del lugar de un delito.

La medición de los cianoacrilatos suspendidos en el aire ha creado problemas, sobre todo en el entorno industrial, donde puede haber interferencias debido a la presencia de un contaminante industrial común, el formaldehído. Actualmente se está validando una técnica de medición que han elaborado los Laboratorios de Salud y Seguridad del Reino Unido.

Utilizando esta técnica de medición no validada, la exposición personal registrada durante la fabricación y utilización de cianoacrilato de etilo en el Reino Unido fue de <0,005 a 0,41 ppm (<0,03-2,1 mg/m³), con un contenido en el 95% de las muestras de menos de 0,19 ppm (0,97 mg/m³). El cianoacrilato de metilo se utilizaba solamente en una de las instalaciones visitadas y la exposición del personal fue inferior al límite de detección en todas las muestras (<0,01 ppm [<0,05 mg/m³]). Debido al carácter ubicuo de los adhesivos de cianoacrilato de metilo y cianoacrilato de etilo en toda la industria, no es posible estimar con exactitud el número de trabajadores potencialmente expuestos, pero cabe suponer que son miles.

Es posible la exposición cutánea durante la fabricación y la utilización de cianoacrilato de metilo y cianoacrilato de etilo. No se ha encontrado información sobre mediciones de la exposición cutánea; sin embargo, cabe prever una exposición baja. La posibilidad de que la piel quede unida a la superficie contaminada hace que, en la práctica, las personas tiendan a tener mucho cuidado cuando trabajan con las sustancias.

Según los datos disponibles, las características toxicológicas principales del cianoacrilato de metilo y el cianoacrilato de etilo parecen derivarse de la actividad local en el punto de contacto. Los datos obtenidos de personas indican que, tras una exposición aislada, el cianoacrilato de metilo y el cianoacrilato de etilo líquidos no son irritantes cutáneos. Sin embargo, hay indicios obtenidos en estudios con personas de que la exposición repetida puede producir efectos de irritación cutánea. Se ha observado irritación ocular en las personas expuestas a adhesivos líquidos de cianoacrilato.

No se pueden sacar conclusiones con respecto al potencial de sensibilización cutánea del cianoacrilato de

metilo; el único estudio disponible no proporcionó ninguna información válida. Para el cianoacrilato de etilo hay varios informes, pero sólo dos contienen datos compatibles con una respuesta de sensibilización cutánea. Hay que tener en cuenta que probablemente es muy difícil realizar estas pruebas con sustancias que se polimerizan rápidamente en la piel; aunque es sólo una teoría, parece plausible que la eliminación del adhesivo endurecido podría contribuir a algunas de las reacciones cutáneas observadas.

Los principales efectos del cianoacrilato de metilo y el cianoacrilato de etilo en la salud observados hasta el momento en relación con la exposición ocupacional son la irritación de los ojos y de las vías respiratorias. Se han notificado varios estudios, tanto de informes de casos como de encuestas en el lugar de trabajo, en los cuales también se ha relacionado la aparición de asma con la exposición al cianoacrilato de metilo y/o el cianoacrilato de etilo. La información disponible no permite sacar conclusiones acerca de si la inducción del asma se debió a un mecanismo alérgico o a uno irritante. En muchas de las pruebas de reto bronquiales, parece que las concentraciones utilizadas eran directamente irritantes.

En un estudio experimental con personas utilizando vapor de cianoacrilato de metilo, no se notificaron efectos irritantes sensoriales con 1 ppm (4,5 mg/m³) (concentración sin efectos adversos observados en el ser humano [NOAEL]); se describió subjetivamente "irritación" de la garganta y la nariz con concentraciones de 2 a 20 ppm (9,1-91 mg/m³) o más. Se notificó irritación y "quemazón" ocular con concentraciones de 4 a 15 ppm (18-68 mg/m³). Con concentraciones superiores a 20 ppm (91 mg/m³), se informó de lagrimación y rinorrea (excepto en un caso en el cual se notificó rinorrea con una concentración de alrededor de 7 ppm [32 mg/m³]), y estos efectos fueron más pronunciados con 50-60 ppm (227-272 mg/m³) (concentración a la cual también se notificó un dolor con quemazón en los ojos). En ausencia de datos cuantitativos semejantes para el cianoacrilato de etilo, dada la estrecha similitud estructural, las propiedades fisicoquímicas parecidas y el perfil toxicológico semejante al cianoacrilato de metilo para la mayor parte de los efectos finales, parecería razonable suponer que también tiene una relación dosis-respuesta similar.

Los datos disponibles sobre la exposición son limitados, en particular para los entornos no ocupacionales. Igualmente, debido a la limitada base de datos toxicológica, es difícil formular observaciones definitivas acerca de los riesgos potenciales para la salud humana.

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