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INTERGOVERNMENTAL NEGOTIATING COMMITTEE FOR AN INTERNATIONAL LEGALLY BINDING INSTRUMENT FOR THE APPLICATION OF THE PRIOR INFORMED CONSENT PROCEDURE FOR CERTAIN HAZARDOUS CHEMICALS AND PESTICIDES IN INTERNATIONAL TRADE
Seventh session
Geneva, 30 October – 3 November 2000
Item 4 (c) of the provisional agenda*

IMPLEMENTATION OF THE PRIOR INFORMED CONSENT PROCEDURE

Note by the secretariat

The first session of the Interim Chemical Review Committee was held in Geneva from 21 to 25 February 2000. The secretariat has the honour to submit to the Intergovernmental Negotiating Committee, annexed to the present note, the report of that session.

* UNEP/FAO/PIC/INC.7/1.

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INTERIM CHEMICAL REVIEW COMMITTEE
First session
Geneva, 21-25 February 2000

REPORT OF THE INTERIM CHEMICAL REVIEW COMMITTEE ON THE WORK OF ITS FIRST SESSION

Introduction

1. The Interim Chemical Review Committee, hereinafter referred to as "the Committee", was established pursuant to decision INC-6/2 of the Intergovernmental Negotiating Committee for an International Legally Binding Instrument for the Application of the Prior Informed Consent Procedure for Certain Hazardous Chemicals and Pesticides in International Trade adopted at its sixth session in July 1999, with a membership of 29 government-designated experts appointed on the basis of the interim prior informed consent (PIC) regions.

2. In accordance with paragraph 7 of that decision and pursuant to the provisions of articles 5, 6 and 7 of the Convention on the Prior Informed Consent (PIC) Procedure for Certain Hazardous Chemicals and Pesticides in International Trade, the functions and responsibilities of the Committee were: to make recommendations on the inclusion of banned and severely restricted chemicals; to make recommendations for the inclusion of severely hazardous pesticide formulations; and to prepare, as appropriate, the relevant draft decision guidance documents.

I. OPENING OF THE MEETING

3. The first session of the Interim Chemical Review Committee was held at the Palais des Nations in Geneva, Switzerland, from 21 to 25 February 2000.

4. The session was opened at 10.15 a.m. on Monday, 21 February 2000 by Ms. Maria Celina de Azevedo Rodrigues (Brazil), Chair of the Intergovernmental Negotiating Committee for an International Legally Binding Instrument for the Application of the Prior Informed Consent Procedure for Certain Hazardous Chemicals and Pesticides in International Trade. She welcomed the participants to the meeting, pointing out that its task was to establish precedents that could serve as a guide in future work on the subject, including the period once the Convention had entered into force.

5. Opening statements were made by the two Executive Secretaries of the interim secretariat, Mr. James Willis, Director of United Nations Environment Programme (UNEP) Chemicals, on behalf of Mr. Klaus Töpfer, Executive Director of UNEP, and Mr. Niek van der Graaff, Chief, Plant Protection Service, Food and Agriculture Organization of the United Nations (FAO), on behalf of Mr. Jacques Diouf, Director-General of FAO.

6. Mr. Willis said that the Committee's first session would set the course for the future technical implementation of the Convention, by serving as a model for the Chemical Review Committee (CRC), which would be set up once the Convention entered into force. The particular task of the CRC was to take action called for under articles 5, 6, 7 and 9 of the Convention. During the interim period, the Committee would be responsible for efforts to implement the interim prior informed consent (PIC) procedure agreed on by Governments in the Final Act adopted in Rotterdam in 1998. At its sixth session, the Intergovernmental Negotiating Committee had also entrusted the Committee with the task of reviewing draft decision guidance documents for four chemicals and revising those draft decision guidance documents, as appropriate, in accordance with the mandate given by the Intergovernmental Negotiating Committee.

7. Mr. van der Graaff said that, at their sessions in October/November 1999, the FAO Council and Conference had welcomed the conclusion of negotiations on the Convention and the resulting secretariat arrangements. Aware of the fragile funding basis for the interim secretariat and the future permanent secretariat, the FAO Conference had requested that additional regular programme funding should be made available for the secretariat. Consequently, FAO had allocated an additional $200,000 to the secretariat for the year 2000. He noted that the Committee’s current session marked a further step towards control of trade in banned or severely restricted pesticides and industrial chemicals. In addition to giving consideration to draft decision guidance documents for four chemicals, the Committee was expected to make recommendations to the Intergovernmental Negotiating Committee on the operational procedures that would govern its work. He urged Governments to assist the secretariat in its work by communicating to it promptly the information called for in the Convention.

II. ELECTION OF THE BUREAU

8. At its opening meeting, the Committee elected the following officers to serve until the expiry of a period of three years or until the first meeting of the Conference of the Parties, whichever should occur first:

Chair:	Mr. Reiner Arndt	(Germany)
Vice-Chairs:	Mr. Dudley Achu Sama	(Cameroon)
	Ms. Flor de María Perla de Alfaro	(El Salvador)
	Mr. Tamás Kömives	(Hungary)
	Mr. Masayuki Ikeda	(Japan)

9. In addition, it was agreed that Mr. Achu Sama would serve as rapporteur.

III. ORGANIZATIONAL MATTERS

A. Attendance

10. At its sixth session, by its decision INC-6/2, the Intergovernmental Negotiating Committee had decided that the Committee should comprise 29 members, designated by Governments, who would serve on an interim basis pending formal confirmation of their appointment by the Intergovernmental Negotiating Committee at its seventh session.

11. Accordingly, the session was attended by the following 26 experts: Mr. Ian Coleman (Australia), Ms. Sandra de Souza Hacon (Brazil), Mr. Dudley Achu Sama (Cameroon), Mr. William James Murray (Canada), Mr. Julio C. Monreal (Chile), Ms. Yong-Zhen Yang (China), Ms. Mercedes Bolaños Granda (Ecuador), Mr. Mohamed El Zarka (Egypt), Ms. Flor de María Perla de Alfaro (El Salvador), Mr. Marc Debois (Finland), Ms. Fatoumata Jallow Ndoye (Gambia), Mr. Reiner Arndt (Germany), Mr. Tamás Kömives (Hungary), Mr. R. R. Khan (India), Mr. Kasumbogo Untung (Indonesia), Mr. Masayuki Ikeda (Japan), Mr. Ravinandan Sibartie (Mauritius), Mr. Mohamed Ammati (Morocco), Mr. Bhakta Raj Palikhe (Nepal), Mr. Karel A. Gijsbertsen (Netherlands), Mr. Hassan A. Al-Obaidly (Qatar), Mr. Boris Kurlyandski (Russian Federation), Mr. William J. Cable (Samoa), Mr. Jan Ferdinand Goede (South Africa), Mr. Azhari Omer Abdelbagi (Sudan) and Ms. Cathleen Barnes (United States of America).

12. Observers from the following parties were also present: Argentina, Australia, Canada, China, Eritrea, European Community, Indonesia, Israel, Japan, Mexico, Morocco, New Zealand, Philippines, Qatar, Switzerland, Ukraine and United States of America.

13. Representatives of the following United Nations bodies and specialized agencies were also present: Secretariat of the Basel Convention.

14. The following non-governmental organizations were also represented: Global Crop Protection Federation (GCPF); Harvard University; International Council of Chemicals Associations (ICCA); and International Union of Food, Agriculture, Hotel, Restaurant, Catering and Allied Workers Associations.

B. Adoption of the agenda

15. At its opening meeting, the Committee adopted the following agenda on the basis of the provisional agenda (UNEP/FAO/PIC/ICRC.1/1) and as amended in the meeting:

1. Opening of the session.

2. Election of the Bureau.

3. Organizational matters:

   (a) Adoption of the agenda;

   (b) Organization of work.

4. Review of the role and mandate of the Interim Chemical Review Committee.

5. Presentation of the prior informed consent procedure.

6. Consideration of draft decision guidance documents referred to the Interim Chemical Review Committee by the Intergovernmental Negotiating Committee for the following four chemicals:

   (a) Ethylene dichloride;

   (b) Ethylene oxide;

   (c) Maleic hydrazide;

   (d) Bromacil.

7. Review of operational procedures for the Interim Chemical Review Committee:

   (a) Making recommendations on the inclusion of banned and severely restricted chemicals;

   (b) Making recommendations on the inclusion of severely hazardous pesticide formulations;

   (c) Preparing draft decision guidance documents;

   (d) Considering a mechanism for collecting and disseminating comments received on draft decision guidance documents as they are developed, so that countries taking a decision based on those documents are fully aware of the reasons behind the control action.

8. Other matters.

9. Adoption of the report.

10. Closure of the meeting.

C. Organization of work

16. At its opening meeting, the Committee decided to conduct its work in plenary and to establish contact groups as the need arose.

IV. REVIEW OF THE ROLE AND MANDATE OF THE INTERIM CHEMICAL REVIEW COMMITTEE

17. The representative of the secretariat introduced the secretariat's note on a review of the role and mandate of the Committee, as presented in document UNEP/FAO/PIC/ICRC.1/2.

V. PRESENTATION OF THE PRIOR INFORMED CONSENT PROCEDURE

18. The representative of the secretariat introduced the secretariat's note on a general presentation of the PIC procedure in the Convention, as contained in document UNEP/FAO/PIC/ICRC.1/3, which set forth the operation of the PIC procedure as set out in articles 4-14 of the Convention.

19. One expert from a developing country drew attention to the difficulty faced by countries such as hers in providing the information required in annex I. In particular, she wondered whether it was really necessary for countries to submit notifications for chemicals already included in the PIC procedure, and for which they had provided an import response; or for which they had no history of use, and which they had already banned. The Chair suggested that the Intergovernmental Negotiating Committee might be requested to consider a procedure whereby, in such cases, it would be sufficient for the country concerned merely to notify the secretariat of its action.

VI. CONSIDERATION OF DRAFT DECISION GUIDANCE DOCUMENTS REFERRED TO THE INTERIM CHEMICAL REVIEW COMMITTEE BY THE INTERGOVERNMENTAL NEGOTIATING COMMITTEE FOR THE FOLLOWING FOUR CHEMICALS

20. In the discussion of the item, it was recognized that the decision guidance documents for ethylene dichloride and ethylene oxide were being recommended in order to conclude outstanding matters under the original PIC procedure and did not in any way constitute a precedent for future notifications and adoption of decision guidance documents under the interim PIC procedure or under the Convention when it entered into force.

A. Ethylene dichloride

21. The representative of the secretariat introduced the background documentation on the sub-item, namely, the secretariat's cover note on consideration of the draft decision guidance documents referred to the Committee by the Intergovernmental Negotiating Committee and the addendum to that note containing the draft decision guidance document for ethylene dichloride (UNEP/FAO/PIC/ICRC.1/4 and Add.1), and also the sections on ethylene dichloride in the compilation of notifications of control actions, background documents and comments on the draft decision guidance documents (UNEP/FAO/PIC/ICRC.1/INF/2 and Add.1). He also drew attention to the exact

mandate conferred upon the Committee by the Intergovernmental Negotiating Committee with respect to ethylene dichloride, in paragraph 2 of its decision INC-6/3, namely, to review the information provided by Governments, regional economic international organizations and interested observers pursuant to that decision, in order to make a further distinction between the industrial and pesticidal uses of ethylene dichloride in the decision guidance document.

22. Following that introduction, the Committee agreed to establish a small drafting group, coordinated by Mr. Achu Sama, to consider the additional information provided in the compilation contained in UNEP/FAO/ICRC.1/INF/2 and Add.1 relating to pesticidal and industrial uses of ethylene dichloride, to incorporate it into the draft decision guidance document and to report back thereon in writing to the plenary. In addition, the drafting group was requested to report back on any matters of principle arising in the course of its discussion.

23. Following the conclusion of the drafting group's work, the coordinator of the drafting group presented the draft decision guidance document on ethylene dichloride as revised by the group and introduced the amendments.

24. The Committee duly decided to entrust the secretariat with the task of incorporating points raised by experts in their discussion of the revised draft. Introducing the updated draft decision guidance document on ethylene dichloride, the representative of the secretariat said that, in accordance with the mandate contained in the decision of the Intergovernmental Negotiating Committee, the draft had been revised so as to specify, wherever possible, the uses of the chemical. He also said that the revised draft incorporated the outcome of discussions in the drafting group and that the draft text would be harmonized in its presentation with that of ethylene oxide, wherever possible. In addition, the draft had been revised to reflect concerns raised and comments made during discussion of the chemical both in the drafting group and in the plenary and the secretariat had endeavoured, in general, to improve the draft document.

25. The Committee's recommendation to the Intergovernmental Negotiating Committee on ethylene dichloride is contained in annex I, and the corresponding revised draft decision guidance document in annex II, to the present report.

B. Ethylene oxide

26. The representative of the secretariat introduced the background documentation on the sub-item, namely, the secretariat's cover note on consideration of the draft decision guidance documents referred to the Committee and the addendum to that note, containing the draft decision guidance document for ethylene oxide (UNEP/FAO/PIC/ICRC.1/4 and Add.2), and also the sections on ethylene oxide in the compilation of notifications of control actions, background documents and comments on the draft decision guidance documents (UNEP/FAO/PIC/ICRC.1/INF/2 and Add.1). He also drew attention to the exact mandate conferred upon the Committee by the Intergovernmental Negotiating Committee with respect to ethylene oxide, in paragraph 2 of its decision INC-6/3, namely, to review the information provided by Governments, regional economic integration organizations and interested observers pursuant to that decision, in order to make a further distinction between the industrial and pesticidal uses of ethylene oxide in

the decision guidance document.

27. Following that introduction, the Committee agreed to establish an open-ended contact group, coordinated by Mr. Murray, to consider the additional information provided in the compilation contained in UNEP/FAO/ICRC.1/INF/2 and Add.1 relating to pesticides and industrial uses of ethylene oxide, to incorporate it into the draft decision guidance document and to report back thereon in writing to the plenary. In addition, the contact group was requested to report back on any matters of principle arising in the course of its discussion.

28. Following the conclusion of the contact group's work, the coordinator of the contact group presented the draft decision guidance document on ethylene oxide as revised by the group and introduced the amendments.

29. The Committee duly decided to entrust the secretariat with the task of incorporating points raised by experts in their discussion of the revised draft. Introducing the updated draft decision guidance document on ethylene oxide, the representative of the secretariat said that, in accordance with the mandate contained in the decision of the Intergovernmental Negotiating Committee, the draft had been revised so as to specify, wherever possible, the uses of the chemical. He also said that the revised draft incorporated the outcome of discussions in the contact group and that the draft text would be harmonized with that of ethylene dichloride, wherever possible. In addition, the draft had been revised to reflect concerns raised and comments made during discussion of the chemical both in the contact group and in the plenary and the secretariat had endeavoured, in general, to improve the draft document.

30. It was noted by one expert that more could have been done to improve the information content of the draft decision guidance document.

31. The Committee's recommendation to the Intergovernmental Negotiating Committee on ethylene oxide is contained in annex I, and the corresponding revised draft decision guidance document in annex II, to the present report.

C. Maleic hydrazide

32. The representative of the secretariat introduced the background documentation on the sub-item, namely, the secretariat's cover note on consideration of the draft decision guidance documents referred to the Committee and the addendum to that note, containing the draft decision guidance document for maleic hydrazide (UNEP/FAO/PIC/ICRC.1/4/Add.3), and also the sections on maleic hydrazide in the compilation of notifications of control actions, background documents and comments on the draft decision guidance documents (UNEP/FAO/PIC/ICRC.1/INF/2 and Add.1). He also drew attention to the exact mandate conferred upon the Committee by the Intergovernmental Negotiating Committee with respect to maleic hydrazide, in paragraph 3 of its decision INC-6/3, namely, to review the chemical, addressing, in particular, the impurity hydrazine and the overall policy issues related to adding chemicals to the PIC procedure on the basis of control actions related to contaminants within the chemical, rather than to the chemical itself and, should it so decide, review and revise, as appropriate, the draft decision guidance document for that chemical for presentation to the Intergovernmental Negotiating Committee at its next

session.

33. Following a discussion of the issue of contaminants and the question of whether chemicals could be included in the PIC procedure on the basis of specified levels of contaminants, rather than the nature of the chemicals themselves, the Committee decided to establish an open-ended contact group on the matter. The contact group was coordinated by Mr. Abdelbagi and Mr. Gijsbertsen.

34. Introducing their report to the Committee, the coordinators of the contact group explained that the group had identified a number of different possible scenarios involving contaminants and their possible effect on the candidature of chemicals for PIC listing of pesticides. Following an extensive discussion of the report, the Committee agreed that there were, essentially, two scenarios: the first, when final regulatory actions to ban a chemical had been taken in at least two countries in two PIC regions on the basis of a contaminant contained in that chemical, and the second, when such regulatory actions had been taken on a chemical on the basis of a specified level of a contaminant. Under the second scenario, the Committee also discussed the situation when product specifications, such as those developed by FAO, were applied on a global scale. Scenarios 3 and 4 were not considered relevant by the Committee. The report of the contact group is attached as annex III to the present report.

35. The Committee agreed that, in the first scenario, the criteria for PIC listing had been met and the chemical would be proposed for inclusion in the PIC procedure. In the second scenario, some experts were of the view that, according to the criteria, no ban or severe restriction had been imposed on the chemical, and it could not therefore be considered for inclusion in the PIC procedure. Many experts, drawing attention to the problem faced by countries in dealing with pesticides, sometimes containing high levels of contaminants, which they lacked the capacity to measure, stressed the need for a mechanism under the Convention to protect such countries against chemicals containing hazardous contaminants. The Committee agreed that the issue was one of policy, involving the interpretation of the terms "chemical", "banned chemical" and "severely restricted chemical", and taking into consideration the aim of the Convention.

36. Accordingly, the Committee decided to refer the issue of chemicals whose use had been banned or severely restricted on the basis of specified levels of contaminants back to the Intergovernmental Negotiating Committee for its further consideration. The Committee also agreed that there might be a need for it to resume its consideration of the issue of contaminants, in the light, first, of discussion of the issue by the Intergovernmental Negotiating Committee and, second, of the outcome of further consideration of other issues relating to maleic hydrazide.

37. One expert noted that the issues associated with maleic hydrazide went beyond a mere consideration of contaminants.

38. The Committee decided not to address the draft Decision Guidance Document on maleic hydrazide until after the seventh session of the Intergovernmental Negotiating Committee.

D. Bromacil

39. The Committee agreed that its deliberations under the sub-item on bromacil would be chaired by Ms. Flor de María Perla de Alfaro, Vice-Chair of the Committee.

40. The representative of the secretariat introduced the background documentation on the sub-item, namely, the secretariat's cover note on consideration of the draft decision guidance documents referred to the Committee and the addendum to that note, containing the draft decision guidance document for bromacil (UNEP/FAO/PIC/ICRC.1/4/Add.4), and also the sections on bromacil in the compilation of notifications of control actions, background documents and comments on the draft decision guidance documents (UNEP/FAO/PIC/ICRC.1/INF/2 and Add.1). He also drew attention to the exact mandate conferred upon the Committee by the Intergovernmental Negotiating Committee with respect to bromacil, in paragraph 4 of its decision INC-6/3, namely, to review the chemical with regard to the basis for the reported control action and the appropriateness of the inclusion of the chemical in the PIC procedure and, should it so decide, review and revise, as appropriate, the draft decision guidance document for that chemical for presentation to the Intergovernmental Negotiating Committee at its next session.

41. Following a discussion of the draft decision guidance document and, specifically, the four notifications that had served as a basis for its preparation, the Committee noted that there was some doubt as to whether the severe restriction reported by Belize and the ban reported by Slovenia were still in force. Moreover, whereas the original expert group had accepted a control action taken in Germany as a justification for proposing the listing of bromacil under the original procedure, further information had since come to light which indicated that the German control action on bromacil had not contained a risk evaluation addressing chemical-specific hazards. For those reasons the Committee felt that the requirements set out in article 5 and annex II of the Convention had not been met, and decided not to recommend inclusion of the chemical in the interim PIC procedure.

42. The Committee also took note of an offer by Mr. Arndt to circulate to all the parties under article 14, paragraph 1 (b), of the Convention the information on bromacil that had been presented during the discussion, as well as information to be provided by the United States of America.

VII. REVIEW OF OPERATIONAL PROCEDURES FOR THE INTERIM CHEMICAL REVIEW COMMITTEE

A. Making recommendations on the inclusion of banned and severely restricted chemicals

B. Making recommendations on the inclusion of severely hazardous pesticide formulations

C. Preparing draft decision guidance documents

D. Considering a mechanism for collecting and disseminating comments received on decision guidance documents as they are developed, so

that countries taking a decision based on those documents are fully aware of the reasons behind the control action

43. The Committee decided to take up the agenda item and its sub-items as a single cluster. During the discussion of the item, a number of general policy issues were raised relating to procedures. To consider those issues more closely, the Committee decided to establish an open-ended contact group on operational procedures. The contact group was coordinated by Mr. Coleman and Mr. Untung.

44. Following the discussion, the Committee decided to assign higher priority to four of the tasks which had been identified by the contact group: first, to revise the notification form pursuant to article 5 so as to make it fully consistent with annex I and revise the guidance of providing information, linking the information to the criteria set out in annex II; second, to prepare a form for proposals pursuant to article 6, based on annex IV, part 1, develop an incident report form and develop guidance on providing information, linking the information to the criteria set out in annex IV, part 3; third, to develop standard formats for decision guidance documents reflecting the needs of countries with respect to import decisions based on the information provided in the notification of final regulatory action (annex I and annex IV); and fourth, to cooperate in and coordinate work on notifications under article 5 and article 6.

45. The Committee also agreed, in order to ensure full participation by all its members, to set up task groups on the four priority tasks identified. As far as possible they would reflect the membership of the PIC regional groups. Annex V to the present report contains the work plan for developing operational procedures for the Committee, together with a list of Committee members who volunteered to participate in the task groups, as well as the expert or organization which would play a lead role in each group.

46. The membership of the task groups on chemicals would consist in the first place of Committee members who had put themselves forward as willing to serve and interested in a particular chemical; subsequently it would be important to ensure fair geographical representation, a task in which the Chair of the Committee and the secretariat would have a useful role to play. Once members had been identified for a particular group, Committee members could be asked by e-mail to endorse their membership. Experts considered that it was also important that the regions from which notifications originated should be represented in the task groups. A number of small groups would be necessary to deal with a large number of chemicals, although, if the workload was light, the work could be entrusted to the Committee as a whole. The task groups would work between sessions of the Committee, keeping in contact by means of e-mail or fax.

47. The Committee also identified the following tasks, to which it assigned lower priority:

(a) To develop guidance on collecting additional information (international assessments) – format, content, resources, delivery of information;

(b) To develop guidance for the secretariat on the collection of the

information listed in annex IV, part 2;

(c) To develop a form for the collection of information from designated national authorities and other relevant bodies (non-governmental organizations, intergovernmental organizations, etc.) under annex IV, part 2;

(d) To revise the import response form;

(e) To develop a guidance document on the operation of the prior informed consent procedure;

(f) To develop a format and contents for a recommendation or recommendations from the Committee to the Intergovernmental Negotiating Committee on the inclusion of a chemical;

(g) To develop a process for drafting decision guidance documents, including deadlines, taking into account the timing stipulated in the Convention.

48. Following consideration of the provisional flow chart (see annex IV to the present report), the Committee decided to approve the chart as put forward by the contact group, and took note of a statement by the Chair of the Intergovernmental Negotiating Committee that it was her intention to invite the Bureau of the Committee to be part of an extended Bureau of the Intergovernmental Negotiating Committee, with a view to strengthening coordination between the two bodies. Various experts made suggestions for changes in the texts on drafting decision guidance documents on banned and severely restricted chemicals and on severely hazardous pesticide formulations.

49. The Committee agreed, furthermore, that, in view of the importance to developing countries and countries with economies in transition of being able effectively to meet the requirements of article 6 on severely hazardous pesticide formulations, full advantage must be taken of all opportunities to collect relevant information.

50. In addition, full advantage should be taken of the large number of training and assistance projects related to pesticides management under way in countries, by providing copies of a guidance document on reporting pesticide poisoning incidents to such projects and encouraging them to make use of that material. A cooperative approach of that kind would facilitate the identification of problematic pesticide formulations and their inclusion in the Convention.

51. Accordingly, the Committee recommended that a one-page incident report form should be developed in conjunction with a simple guidance document on the completion of the form and the development of proposals in line with article 6 and annex IV, part I, of the Convention. The guidance document would also provide reference to the use of the information relevant to the Convention and request that the information be forwarded to the secretariat.

52. The recommendation to the Intergovernmental Negotiating Committee on the one-page incident report form is contained in annex I to the present report.

53. The recommendation to the Intergovernmental Negotiating Committee on assistance to countries in identifying severely hazardous pesticide formulations is contained in annex I to the present report.

VIII. OTHER MATTERS

A. Request to the secretariat

54. The secretariat was requested to produce a compilation of examples of notified bans and severe restrictions applying to pesticides or to industrial chemicals, to provide experts with an indication of the variety of actions on which notifications were submitted.

B. Dates for the second session of the Committee

55. Concerning the matter of the second session of the Committee, it was pointed out that the funds currently available to the secretariat might be sufficient to permit a further session of the Intergovernmental Negotiating Committee, or of the Committee, but not both. Given the desirability of maintaining the momentum that had been built up at its first session, however, it was agreed that a second session of six or seven days should be held as soon as possible after the next session of the Intergovernmental Negotiating Committee, if resources permitted. The Committee noted that there was a possibility of a second session at the end of 2000 or in early 2001. If the workload proved to be large, the Intergovernmental Negotiating Committee could be informed that a further session would be needed.

IX. ADOPTION OF THE REPORT

56. The present report was adopted on the basis of the draft report, which had been circulated to experts in documents UNEP/FAO/PIC/ICRC.1/L.1 and Add.1, and on the understanding that finalization of the report would be entrusted to the secretariat working in consultation with the Rapporteur.

X. CLOSURE OF THE SESSION

57. Following the customary exchange of courtesies, the Chair declared the session closed at 5 p.m. on Friday, 25 February 2000.

Annex I

RECOMMENDATIONS TO THE INTERGOVERNMENTAL NEGOTIATING COMMITTEE, ADOPTED BY THE INTERIM CHEMICAL REVIEW COMMITTEE AT ITS FIRST SESSION, GENEVA, 21-25 FEBRUARY 2000

A. Ethylene dichloride

The Interim Chemical Review Committee recommends that the Intergovernmental Negotiating Committee adopt the draft decision guidance document for the chemical ethylene dichloride contained in annex II to the report of the Committee on the work of its first session, with the effect that the chemical becomes subject to the interim PIC procedure as it is defined in paragraph 2 of the resolution on interim arrangements.

B. Ethylene oxide

The Interim Chemical Review Committee recommends that the Intergovernmental Negotiating Committee adopt the draft decision guidance document for the chemical ethylene oxide contained in annex II to the report of the Committee on the work of its first session, with the effect that the chemical becomes subject to the interim PIC procedure as it is defined in paragraph 2 of the resolution on interim arrangements.

C. Incident report form

The Interim Chemical Review Committee recognizes the need to develop a one-page incident report form in conjunction with a simple guidance document on the completion of the form and the development of proposals in line with article 6 and annex IV, part I, of the Convention. The Committee therefore recommends that the Intergovernmental Negotiating Committee should encourage States, bilateral and multilateral aid agencies, intergovernmental organizations and non-governmental organizations to make use of the incident report form and guidance document on reporting pesticide poisoning incidents in their projects.

D. Assistance to countries in identifying severely hazardous pesticide formulations

The Committee recommends that the Intergovernmental Negotiating Committee encourage States, bilateral and multilateral aid agencies and non-governmental organizations to assist developing countries and countries with economies in transition in implementing specific projects to identify severely hazardous pesticide formulations causing problems under conditions of use in those countries.

E. Contaminants

The Committee recommends that the Intergovernmental Negotiating Committee adopt a policy on contaminants which would include final regulatory actions to ban a pesticide that had been taken by at least two countries in two PIC regions on the basis of a contamination contained in that substance, where the notification also met the requirements of annexes I and II of the Convention.

Annex II

DRAFT DECISION GUIDANCE DOCUMENTS
REVISED BY THE INTERIM CHEMICAL REVIEW COMMITTEE
AT ITS FIRST SESSION

A. Ethylene dichloride

DRAFT

PIC - Decision guidance document for a banned or severely restricted chemical

Ethylene dichloride

Published:

Common name	Ethylene dichloride (ISO)
Other names/ Synonyms	1,2-Dichloroethane (IUPAC, CA); alpha,beta-dichloroethane; 1,2-bichloroethane; ethane dichloride; ethane, 1,2-dichloro-; ethylene chloride; EDC; 1,2-ethylene dichloride; sym-(metric)-dichlorethane.
CAS No.	107-06-2
Use category	Pesticide
Use	Ethylene dichloride is reported used as both a pesticide and an industrial chemical. **Pesticide use**: A small fraction of the total production (approximately 0.1% in the USA in 1977) was used for pesticide solvent and as an insecticidal fumigant, mainly in stored products. When used as a fumigant, ethylene dichloride is usually mixed with carbon tetrachloride to reduce the fire hazard, and small portions of other fumigants may be added *(WHO, 1987)*. It was also used as a rodenticide. **Industrial use**: The major industrial use of the compound is in the synthesis of vinyl chloride (approximately 90% of the total production in Japan and approximately 85% of total production in the USA). Other chemicals produced from ethylene dichloride are 1,1,1-trichloroethane, ethyleneamines, vinylidene chloride, trichloroethylene, tetrachloroethylene and ethylene glycol. In 1977, 2 - 4% of the total production of ethylene dichloride in the USA was used for the synthesis of each of these chemicals. Another 2% was used in the USA as a lead scavenger in gasoline (*WHO, 1987*). It is also used as laboratory solvent, as a drying agent in glues and for the fusion of plastics.
Trade names	Borer-Sol, Brocide, Destruxol, Dichlor-emulsion, Dichlor-mulsion, Dutch Liquid, Dutch Oil, ENT 1656, Gaze Olefiant.
Formulation types	Liquid
Basic manufacturers	Dow Chemicals USA; Vulcan Materials Company, USA

Reasons for inclusion in the PIC procedure

Ethylene dichloride is included in the PIC procedure based on reported bans and severe restrictions on its use as a pesticide[1]. No control actions have been reported relating to its industrial uses. Inclusion was recommended at the eighth meeting of the FAO/UNEP Joint Group of Experts on Prior Informed Consent following detailed discussions during the sixth and seventh meetings.

[1] Users of the DGD should be aware that the term "pesticides" may have different meanings in different jurisdictions.

Summary of control actions (see Annex 2 for details)

Control actions were reported by 6 countries and the European Union. In 5 countries (Austria, Belize, Canada, Slovenia and the United Kingdom) and in the European Union, ethylene dichloride was reported as banned for use as an agricultural pesticide. No remaining uses in agriculture were reported. Thailand reported that ethylene dichloride was totally banned for the fumigation of stored products. Concern about the carcinogenic properties of ethylene dichloride on human health is reported as a primary reason for the control actions.

Hazard classification by organization

WHO	Gaseous or volatile fumigant not classified under the WHO recommended classification of pesticides by hazard (*IPCS , 1998-1999*)
EPA	Group B2 (probable human carcinogen). *(USEPA, 1991).*
EU	F; R11|carc. Cat. 2; R45|Xn; R 22|Xi; R 36/37/38 (classification in accordance with Directive 67/548/EEC on the approximation of the laws, regulations and administrative provisions relating to the classification, packaging and labelling of dangerous substances, 12th ATP, 1991).
IARC	Group 2B (possibly carcinogenic to humans). *(IARC, 1999).*

Protective measures that have been applied concerning the chemical

Measures to reduce exposure

For the health and welfare of workers and the general public, the handling and application of the substance should be entrusted only to competently supervised and well-trained applicators who must follow adequate safety measures and use the chemical according to good application practices. Regularly exposed workers should receive appropriate monitoring and health evaluations. Protective clothing as indicated in the *FAO Guidelines for Personal Protection when Working with Pesticides in Tropical Climates* (1990) is required.

In view of the volatility of ethylene dichloride, particular attention should be given to control inhalation exposure.

Packaging and labelling

Follow the *FAO Revised Guidelines on Good Labelling Practice for Pesticides (1995)* and the *Guidelines for the Packaging and Storage of Pesticides* (1985). Unbreakable packaging required; put breakable packaging into closed unbreakable container. Do not transport with food and feed stuff.

The United Nations Committee of Experts on the Transportation of Dangerous Goods classifies the chemical in:

Hazard class: 3

Packing group: II

Alternatives

Only Austria reported that many alternatives for designated purposes were available. No alternatives were reported by other notifying countries.

It is essential that before a country considers substituting any of the reported alternatives, it ensures that the use is relevant to their national needs.

Waste Disposal

Waste should be disposed of in accordance with the provisions of the Basel Convention on the Control of Transboundary Movements of Hazardous Wastes and Their Disposal**,** any guidelines thereunder *(SBC, 1994)* and any other relevant regional agreements.

See the *FAO Guidelines on Prevention of Accumulation of Obsolete Pesticide Stocks (1995),* and *The Pesticide Storage and Stock Control Manual* (1996)*.*

Wear protective clothing and respiratory equipment suitable for hazardous materials. Sweep, scoop or pick up spilled material. Vacuuming or wet sweeping may be used to avoid dust dispersal. Do not flush to surface water or sanitary sewer system. Dispose of empty containers in a sanitary landfill or by incineration.

Waste must never be discharged into sewers or surface waters. Contaminated porous surfaces (sand, vemiculite, etc) should be disposed of at a waste management facility. Recovered liquids may be reprocessed, incinerated or treated at a waste management facility (*Environment Canada, 1992*).

It should be noted that the methods recommended in the literature are often not suitable in a specific country. High temperature incinerators may not be available. Consideration should be given to the use of alternative destruction technologies.

Exposure limits

	Type of limit	**Value**
Food	MRL's (Maximum Residue Limits in mg/kg) in specified products *(FAO/WHO, 1999).*	No MRL allocated.
	JMPR ADI (Acceptable Daily Intake) in mg/kg diet *(WHO, 1992).*	No ADI allocated.
Workplace	USA TLV-TWA (Threshold Limit Value; Time-Weighted Average)*(ACGIH, 1999)*.	10 ppm (40 mg/m^3)

First aid

First aid: Move victim to fresh air. Call emergency medical care. Apply artificial respiration if victim is not breathing. Administer oxygen if breathing is difficult. Remove and isolate contaminated clothing and shoes. In case of contact with substance, immediately flush skin or eyes with running water for at least 20 minutes. Wash skin with soap and water. Keep victim warm and quiet. Effects of exposure (inhalation, ingestion or skin contact) to substance may be delayed. Ensure that medical personnel are aware of the material(s) involved, and take precautions to protect themselves (*U.S. Department of Transportation, 1996*).

Annexes

Annex 1 **Further information on the substance**

Annex 2 **Details on reported control actions**

Annex 3 **List of designated national authorities**

Annex 4 **References**

Annex 1 - Further information on the substance

1 Chemical and physical properties

1.1	**Identity**	Clear colourless liquid; chloroform-like odour; sweet taste *(Tomlin, 1994).*
1.2	**Formula**	$C_2H_4Cl_2$
	Chemical name	1,2-dichloroethane (CA).
1.3	**Solubility**	5-10 mg/ml at 19°C in water
	logP_{ow}	1.76
1.4	**Vapour pressure**	8.53 kPa (64 mmHg), 20 °C, highly volatile.
1.5	**Melting point**	-36°C
1.6	**Boiling point**	83.5°C
1.7	**Flammability**	It is flammable. The flash point is 13°C
1.8	**Reactivity**	This compound is incompatible with strong alkalis, strong caustics, oxidizing materials, active metals such as aluminium, magnesium, sodium or potassium. It reacts violently with nitrogen tetraoxide, dimethylaminopropylamine or liquid ammonia. A vigorous reaction also occurs when a mixture of this compound, propylene dichloride and o-dichlorobenzene comes into contact with aluminium. It can corrode iron, zinc and aluminium in the presence of moisture *(Sax, 1986)*. Mixtures with nitric acid easily deteriorate *(Bretherick, 1986)*.

2 Toxicity

2.1 General

2.1.1	**Mode of action**	Although only limited quantitative data are available, inhaled ethylene dichloride is likely to be adsorbed by the lungs in humans and experimental animals, based on its high vapour pressure and serum/air partition coefficient *(WHO, 1994)*.
2.1.2	**Uptake**	Ethylene dichloride can be found in the blood of rodents, almost immediately after dermal, oral or inhalation exposure. Peak blood level in rat during dermal exposure for 24 hours is 135 mg/l *(Morton, 1991 in Richardson, 1993).*
2.1.3	**Metabolism**	Ethylene dichloride is metabolised in rat and mouse by two competing pathways, both of which involve glutathione (GSH). Oxidation gives chloroacetaldehyde which is detoxified by GSH; it also reacts with GSH to form S-(2-chloroethyl)glutathione*(D'sruza, 1988 in Richardson, 1993)*. Following intraperitoneal injection of mouse, the alkyl purines 7-(2-oxoethyl)guanine and 7-[S-(2-cysteinyl)ethyl]guanine were found in DNA hydrolizates and in the urine. Chloroacetaldehyde and S-(2-chloroethyl)glutathione were found in haemoglobin *(Svensson, 1986 in Richardson, 1993).* Following intraperitoneal injection of 50-170 mg/kg ^{14}C-ethylene dichloride to mice, 10-42% was expired unchanged and 12-15% as carbon dioxide. Most of the remainder was excreted in the urine, primarily as chloroacetic acid (via chloroacetaldehyde), S-(carboxymethyl)cysteine and thiodiacetic acid *(Yllner,*

1971 in Richardson, 1993).

Little dechlorination of ethylene dichloride was found to occur in rat and rabbit liver preparations in vitro *(Rannug, 1978 in Richardson, 1993)*.

Metabolism of ethylene dichloride appears to have a significant role in the manifestation of the toxic, carcinogenic and mutagenic effects of this chemical.

2.2 Known effects on human health

2.2.1 Acute toxicity

Symptoms of poisoning

Breathing ethylene dichloride can irritate the nose, throat and lungs causing coughing, shortness of breath and difficulty in breathing. Higher levels can cause a build-up of fluid in the lungs (pulmonary oedema). This can cause death. Exposure can cause nausea, vomiting, headaches, increasing drowsiness and then loss of consciousness. Over-exposure can also cause liver and kidney damage, and irritate the eyes. Contact can irritate the skin causing redness and a rash, and irritate the eyes *(USEPA, 1987)*.

The lethal oral dose of ethylene dichloride in humans has been estimated to be between 20 and 50 ml *(WHO, 1994)*.

2.2.2 Short and long term exposure

Cancer Hazard: Ethylene dichloride may be a carcinogen in humans since it has been shown to cause stomach, lung, breast and other types of cancer in animals.

Other long term effects: Ethylene dichloride can irritate the lungs. Repeated exposure may cause bronchitis to develop with cough, phlegm and/or shortness of breath. Repeated, prolonged contact can chronically irritate the skin causing dryness, redness and a rash. Repeated, prolonged exposure can cause loss of appetite, nausea and vomiting, trembling and low blood sugar (with weakness). It may damage the liver and kidneys *(USEPA, 1987)*.

2.2.3 Epidemiological studies

Significant excess of deaths due to pancreatic cancer was found in a study of 278 men working in the chlorohydrin unit of a chemical production plant between 1941 and 1967 *(Benson & Teta 1993 in WHO, 1995)*.

No significant difference was found compared with control in a case-control study on 21 employees at a petrochemical plant in USA *(WHO, 1994)*.

In a cohort study of 6588 workers at the same plant, no significant excess of malignant brain tumours was observed *(Austin & Schnatter, 1983 in WHO, 1995)*.

No association between ethylene dichloride spill and leukemia in childhood was found in a small case-control study *(Deschamps & Band, 1993 in WHO, 1995)*.

A statistically significant increase in colon and rectal cancer was observed in men aged $\geq$ 55 years and whose drinking water contained $\geq$ 0.1 µg/l ethylene dichloride, even if the authors did not suggest an association between ethylene dichloride and cancer but underlined the higher rectal cancer incidence in populations consuming chlorinated water *(Isacson, 1985 in WHO, 1995).*

Higher prevalence of subjective symptoms was observed in 10 male workers in an oil refinery exposed to 250-800 mg/m^3 than in those exposed to lower concentrations. However there was a co-exposure to benzene *(Cetnarowicz, 1959 in WHO, 1995).*

An increased morbidity for all disease categories was observed in a 5-year period (1951-55) in a group of workers at an aircraft factory exposed for 25-30% of the working time to 80-150 mg/m^3 and to ≤ 5 mg/m^3 for the remainder *(Kozik, 1957 in WHO, 1995)*.

2.3 Toxicity studies with laboratory animals and *in vitro* systems

2.3.1 Acute toxicity

oral LD_{50} for rats, mice, dogs and rabbits ranged from 413 to 2500 mg/kg bw *(WHO, 1995)*.

Dermal LD_{50} for rabbits ranged from 2800 to 4900 mg/kg bw *(Torkelson & Rowe, 1981 in WHO, 1995).*

Inhalation LC_{50} for rats exposed for 6 or 7.25 hours ranged from 4000 mg/m^3 to 6600 mg/m^3 *(WHO, 1995)*.

Irritation Application of ethylene dichloride to the skin of experimental animals has resulted in microscopic changes and moderate oedema *(Duprat et al., 1976).*

2.3.2 Short-term-exposure

Several short-term and subchronic studies in different experimental species indicate that liver and kidneys are the target organs. The documentation was considered inadequate to derive NOELs or LOELs. Some studies show morphological changes in the liver in several species following subchronic exposure to airborne concentrations as low as 800 mg/m^3. Liver weight increase was observed in rats with subchronic oral administration of 49 to 82 mg/kg bw. Changes in serum parameters that indicate liver and kidney toxicity were observed in rats exposed to airborne concentrations as low as 202 mg/m^3 for 12 months *(WHO, 1995).*

2.3.3 Long-term exposure

Studies on the chronic effects are related to the carcinogenicity of the substance and do not give sufficient information on non-neoplastic effects of the substance. Ethylene dichloride was carcinogenic in mice and rats when administered by gavage or dermal application, while no increase in the incidence of tumours was noted in inhalation or in initiation/promotion bioassays *(WHO, 1994)*.

2.3.4 Effects on reproduction

There is no evidence from a limited number of studies that ethylene dichloride is teratogenic in experimental animals. There is also little convincing evidence that ethylene dichloride induces reproductive or developmental effects at doses below those which cause other systemic effects *(WHO, 1995)*.

2.3.5 Mutagenicity

Ethylene dichloride has been consistently positive in *in vitro* mutagenic bioassays in *Salmonella typhimurium*. Response has been greater in the presence of an exogenous activation system (cytochrome P450 system) than in its absence, and mutagenicity was more than doubled in *S. thyphimurium* expressing the human GSTA-1 gene. In cultured mammalian cells, ethylene dichloride forms DNA adducts. It also induces unscheduled DNA synthesis in primary cultures of rodents and human cells and gene mutation in several cell lines. Mutation frequency in human cell lines has been correlated with differences in glutathione-S-transferase activity. In *in vivo* studies ethylene dichloride induced somatic cell and sex-linked recessive lethal mutations in *Drosophila melanogaster* and the compound bound to DNA in all reported studies in rats and mice. Although primary DNA damage in liver and sister chromatid exchange has been observed in studies in mice, there has been no evidence for micronucleus induction *(WHO, 1995)*.

2.3.6 **Carcinogenicity**

Carcinogenicity of ethylene dichloride was investigated in a few limited bioassays on experimental animals. Significant increases were not found for any type of tumour in Sprague-Dawley rats or Swiss mice exposed to up to 607 mg/m^3 for 78 weeks (a high mortality was observed in this study although it was not related to concentration). No significant increase in the incidence of mammary gland adenomas and fibroadenomas in Sprague-Dawley females exposed to 200 mg/m^3 for 2 years *(WHO, 1995)*.

Significant increased incidence of tumours was observed in two species following ingestion; squamous cell carcinomas of the stomach in males, haemangiosarcomas in both sexes. Fibromas of the subcutaneous tissue in males, adenocarcinomas and fibroadenomas of the mammary gland in females were observed in Osborne-Mendel rats with Time-Weighted Average (TWA) daily doses of 45 to 95 mg/kg bw/day for 78 weeks. Similar increases in alveolar/bronchiolar adenomas in males and females, mammary gland adenocarcinomas in females and endometrial stromal polyp or endometrial stromal sarcoma combined in females and hepatocellular carcinomas in males were observed in B6C3F1 mice administered TWA of 97 or 195 mg/kg bw/day for males and 149 or 299 mg/kg bw/day for females by gavage for 78 weeks *(WHO, 1995).*

A significant increase of lung tumours (benign papillomas) was found in female mice following repeated ethylene dichloride application for 440 to 594 days. A dose-related increase in the incidence of pulmonary adenomas was found in mice following repeated intraperitoneal injection of ethylene dichloride but was not significant. Concomitant exposure to inhaled ethylene dichloride and disulfuram in the diet resulted in an increased incidence of intrahepatic bile duct cholangiomas and cysts, subcutaneous fibromas, hepatic neoplastic nodules, interstitial cell tumours in the testes and mammary adenocarcinomas in rats compared to rats administered either the compound alone or untreated controls. A further three bioassays did not show evident tumour development initiating or promoting properties *(WHO, 1995)*.

3 Exposure

3.1 **Food**

Very little information is available on ethylene dichloride in food. Ethylene dichloride was found in Germany in milk products with added fruits. In Canada it was used as an extractant in samples of spice oleoresins. Residue studies show that ethylene dichloride can be found in fumigated grain *(WHO, 1987)*.

3.2 **Occupational**

Ethylene dichloride levels of up 150 mg/m^3 and ranging from 40 to 800 mg/m^3 were detected in industrial plants using the chemical as a solvent *(WHO, 1987)*.

Time-weighted averages of 0.1 and 1 mg/m^3, respectively, have been reported for two different jobs in an anti-knock agent blending plant in the USA. The maximum exposure level measured was 8.9 mg/m^3 *(WHO, 1987)*.

3.3 **Environment**

Owing to the limited releases of ethylene dichloride, it is a rare environmental contaminant. It has been detected in both surface and groundwaters, but unlike other volatile organic compounds (VOCs), higher levels were reported in surface waters. USEPA estimates that 0.3% of all groundwater supplies contain ethylene dichloride concentrations ranging from 0.5 to 5.0 g/l. Three percent of surface waters are estimated to have concentrations from 0.5 to 20 g/l *(Howard, 1990; USEPA, 1987)*.

Ethylene dichloride commonly occurs in the air of urban and suburban areas at concentrations less than 0.2 ppb. The greatest source of ethylene dichloride exposure is from the air. Drinking water is the greatest source for populations with drinking water levels above 6 g/l *(Howard, 1990; USEPA, 1987)*.

3.4 **Accidental poisoning**

Acute incidental exposure to ethylene dichloride by inhalation or ingestion has resulted in a variety of effects in humans, including effects on the central nervous system, liver, kidney, lung and cardiovascular system.

4 Effects on the environment

4.1 Fate

Ethylene dichloride released to the air slowly degrades over a period of a few months. Photo-oxidation with hydroxyl radicals, that results in the production of carbon dioxide and hydrochloric acid, is believed to be the predominant removal process. It is expected that ethylene dichloride is transported over long distances and washed out during rainfall. Direct photolysis is not expected to occur *(Howard, 1990)*.

Ethylene dichloride released to surface waters will be removed primarily by evaporation within a few days or weeks. Adsorption to sediment and hydrolysis is not expected.

Releases of ethylene dichloride on to soil will evaporate fairly rapidly. Rapid migration to groundwater is expected for sandy soils *(Howard, 1990)*.

4.1.1 **Persistence**

Biodegradation is not expected to occur under either aerobic or anaerobic conditions. The photo-oxidation of ethylene dichloride in air is expected to be a slow process. No significant bioaccumulation is expected to occur in aquatic organisms *(Howard, 1990)*.

4.1.2 **Bioconcentration**

Ethylene dichloride is not expected to bioconcentrate in fish due to its low Kow. The measured bioconcentration factor for bluegill sun fish is 0.30 (*Richardson, 1993*).

4.2 Ecotoxicity

4.2.1 **Fish**

Acute toxicity studies have been conducted on several species of freshwater fish. The most sensitive species was two to three-month old guppies *(Poecilia reticulata)*, with a nominal 7-day LC_{50} of 106 mg/l ethylene dichloride under static renewal test conditions. In three studies in 30-day old fathead minnows *(Pimephales promelas)* over 96-hour LC_{50} values ranged from 116 to 136 mg/l under flow-through conditions. The only adequate acute toxicity study in marine fish involved tidewater silversides *(Minidia beryllina)* in which a nominal 96-hour LC_{50} of 480 mg/l was reported under static test conditions *(WHO, 1994)*.

In a long-term flow-through study of the early life stages of fathead minnows *(Pimephales Promelas)* a NOEL of 29 mg/l and a LOEL of 59 mg/l (reduced larval growth) were identified *(WHO, 1994)*. The EC_{50} for hatchability and a 27-day LC_{50} for post-hatch survival both of 34 mg/l, resulted from an ethylene dichloride flow-through assay on embryos and larvae of rainbow trout *(Onchorhyncus mykiss)* and the LOEL identified was 3.49 mg/l (24% reduction in egg hatchability) *(WHO, 1994)*.

After 21 days of continuous exposure to 150 mg/l ethylene dichloride, mortality of coho salmon *(Onchorhyncus kisutch)* eggs was 46%, while in alevins, 100% mortality occurred 9 days after hatching at 320 mg/l *(WHO, 1994)*.

Teratogenic effects were observed in rainbow trout *(Onchorhyncus mykiss).*

4.2.2 **Aquatic invertebrates**

Daphnia magna appear to be the invertebrate species most sensitive to ethylene dichloride in chronic toxicity studies in freshwater. Under static conditions, the measured 48-hour LC_{50} values for fed and unfed first instar *Daphnia* were 320 and 270 mg/l, respectively; the 48-hour LC_{50} based on complete immobilization, were 180 and 160 mg/l for fed and unfed organisms, respectively *(WHO, 1994)*.

In a 28-day flow-through study on *Daphnia magna* the LOEL and NOEL for reproductive success were respectively 20.7 and 10.6 mg/l, while the LOEL and NOEL for growth were 71.7 and 41.6 mg/l *(WHO, 1994)*.

With regard to acute toxicity studies in marine invertebrates under static test conditions, the nominal 24-hour EC_{50} for immobilization of 30-hour posthatch larvae of the brine shrimp, *Artemia salina*, was 93.6 mg/l *(WHO, 1994)*. For marine adult shrimp, *Crangon crangon*, the measured 24-hour LC_{50} was 170 mg/l, under static test conditions *(WHO, 1994)*.

4.2.3 **Birds**

Significant reduction of the egg weight at 250 mg/kg and reduction of both the number and weight of eggs at 500 mg/kg were observed in a study in which male and female leghorn chickens were fed mash which had been fumigated with ethylene dichloride *(WHO, 1994)*.

4.2.4 **Bees**

There are no adequate studies to permit an assessment of effects on bees.

4.2.5 **Other**

Aquatic micro-organisms

The IC_{50}s for *Nitrosomonas* and methanogens (29 and 25 mg/l, respectively) were considerably lower than for aerobic heterotrophs (470 mg/l). For the bacteria, *Pseudomonas putida*, the nominal 16-hour EC_{50} for the onset of cell multiplication inhibition was 135 mg/l *(WHO, 1994)*.

The freshwater blue-green algae, *Microcystis aeruginosa*, was seven times more sensitive to ethylene dichloride than green algae, *Scenedesmus quadricauda*, with a nominal 7-day ED_{50}s for inhibition of cell miltiplication at 27 °C of 105 and 710 mg/l, respectively *(WHO, 1994)*.

Based on bioluminescence, the 5-minute IC_{50} was 700 mg/l in a Microtox test with *Photobacterium phosphoreum (WHO, 1994)*.

Aquatic vertebrates

In a study in which embryos and larvae of the northwestern salamander (*Ambystoma gracile*) and the leopard frog (*Rana pipiens*) were continuously exposed to ethylene dichloride from 30 minutes of fertilization (embryos) and maintained through four days posthatching (larvae), the resulting LC_{50}s for the salamander were 6.53 mg/l at the day of hatching (day 5) and 2.54 mg/l 4-day posthatching (day 9). LOEL was 0.99 mg/l for 23% reduction in egg

	hatchability. The measured 5-day and 9-day LC_{50} values for the frog were 4.52 and 4.40 mg/l respectively, while the 5-day posthatch LOEL was 1.07 mg/l *(WHO, 1994)*.
Terrestrial invertebrates	In an acute contact test, a 48-hour LC_{50} for earthworms (*Esinia fetida*) exposed to ethylene dichloride-treated filter paper was 60 μg/m^2 *(WHO, 1994)*.
Plants	Ethylene dichloride vapour was both lethal and mutagenic to barley kernels (two-rowed variety, *Bonus*) following exposure to 3 mg/m^3 for 24 hours.

Annex 2 - Details on reported control actions

AUSTRIA

Effective: 1992.

Control action: All agricultural uses banned.

Reasons: Carcinogenic and mutagenic properties. The substance has a potential for reproductive effects in males and central nervous system effects.

Alternatives: Many alternatives for designated purposes.

BELIZE

Effective: 1985.

Control action: The substance is banned for agricultural use.

Reasons: Mixed with CCl_4, a carcinogen.

CANADA

Effective: 1984.

Control action: Suspended/banned for agricultural use.

EUROPEAN UNION

Effective: 1989.

Control action: The placing on the market and the use of plant protection products containing 1,2-dichloroethane is prohibited. No remaining uses in agriculture allowed.

Reasons: The use of 1,2-dichloroethane as a plant protection product, in particular to fumigate plants and soil, is likely to give rise to harmful effects on human and animal health as well as unreasonable adverse influence on the environment. 1,2-dichloroethane has been classified by the European Community as a category 2 carcinogen (probably carcinogenic to humans).

(Member States of the European Union are: Austria, Belgium, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Luxembourg, Netherlands, Portugal, Spain, Sweden, United Kingdom.)

SLOVENIA

Effective: 1997.

Control action: Banned for use in agriculture.

Reasons: This chemical was banned from the use in agriculture due to the effect of its toxic properties to human health and the environment according to the opinion given by the Commission on Poisons.

THAILAND

Effective: **1995**

Control action: Ethylene dichloride was totally banned for the export, import, production or having in possession as a pesticide. Use of Ethylene dichloride for fumigation of stored products was totally banned by the final regulatory action. Industrial use as a raw material in manufacture of vinylchloride remains allowed.

Reasons: Possible carcinogen.

UNITED KINGDOM

Effective: 1989.

Control action: All agricultural uses revoked under the Control of Pesticides Regulations.

Reasons: Evidence of carcinogenicity.

Annex 3 – List of Designated National Authorities

AUSTRIA

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CP **DNA** Industrial Chemicals and Pesticides
P **DNA** Pesticides
C **DNA** Industrial Chemicals

Annex 4 - References

AMERICAN CONFERENCE OF GOVERNMENTAL INDUSTRIAL HYGIENISTS (ACGIH). (1999). Guide to Occupational Exposure Values. Cincinnati, OH: Publications Office, ACGIH.

BRETHERICK, L., Ed. (1986). Hazards in the Chemical Laboratory. 4th Ed. The Royal Society of Chemistry, London, p. 280.

DUPRAT, P. *et al*. (1976). Pouvoir irritant des principaux solvants chlores aliphatiques sue la peau et les muqueuses oculaires du lapin. *European Journal of Toxicology*, 9: 171-177.

ENVIRONMENT CANADA. (1992). Tech Info for Problem Spills: Ethylene Dichloride (draft), p.106-107.

FAO/WHO (1999). Pesticide residues in food - 1998. Report of the Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Toxicological Care Assessment Group on Pesticide Residues. FAO Plant Production and Protection Paper 140. Food and Agriculture Organization, Rome.

HAYES, W.J., Jr. (1982). Pesticides Studied in Man. Williams and Wilkins, Baltimore, p. 150-152.

HOWARD, P.H. (1990). Handbook of Environmental Fate and Exposure Data for Organic Chemicals, Volume II. Chelsea Michigan: Lewis Publishers, p. 153-159.

HSDB. Hazardous Substances Data Bank. Bethesda, MD: National Library of Medicine (file on-line).

IARC (1999). Monographs on the evaluation of the carcinogenic risk of chemicals to man. Geneva: World Health Organization, International Agency for Research on Cancer, V71.

IPCS (1998-1999). The WHO Recommended Classification of Pesticides by Hazard and Guidelines to Classification. International Programme on Chemical Safety 1998-1999, Table 7 p.37.

MORTON, G.W. M.D. (1986). Toxicology of the Eye. 3rd Ed. Charles C. Thomas, Publisher. Springfield, IL, p. 323-325.

RICHARDSON. M.L. ED. (1993). Dictionary of Substances and their Effects.

SAX, N. I., Ed. (1986). Hazardous Chemicals Information Annual, No. 1. Van Nostrand Reinhold Information Services, New York, p. 433-440.

SBC (1994). Basel Convention on the Control of Transboundary Movements of Hazardous Wastes and Their Disposal. Secretariat of the Basel Convention, SBC No. 94/008.

TOMLIN, C. (1994). Pesticide manual, a world compendium (10th Ed.). British Crop Protection Council, Surrey, England.

U.S. DEPARTMENT OF TRANSPORTATION (1996). North American Emergency Response Guidebook. A Guidebook for First Responders During the Initial Phase of Hazardous Materials/Dangerous Goods Incident. U.S. Department of Transportation Research and Special Programs Administration, Office of Hazardous Materials Initiatives and Training (DHM-50), Washington, D.C. (1996),p. G-129.

USEPA. (1987). Health Advisory-1,2-Dichloroethane, Office of Drinking Water. United States Environmental Protection Agency.

USEPA (1991). USEPA IRIS Substance File Online: 1,2-Dichloroethane. United States Environmental Protection Agency.

WHO (1987). Environmental Health Criteria n. 62: Dichloroethane. IPCS, World Health Organization, Geneva.

WHO (1992). Evaluation of certain food additives and naturally occurring toxicants. Thirty ninth report of the Joint FAO/WHO Expert Committee on Food Additives. World Health Organization (WHO Technical Report Series No. 828) (Geneva).

WHO (1994). Environmental Health Criteria. First Draft April, 1994 Internal Technical report.

WHO (1995). Environmental Health Criteria 176, 1,2-Dichloroethane (2nd Edition). IPCS, World Health Organization, Geneva.

B. Ethylene oxide

DRAFT

PIC - Decision guidance document for a banned or severely restricted chemical

Ethylene oxide

Published:

Common name	Ethylene oxide (ISO)
Other names/ synonyms	oxirane (CA, IUPAC); dihydrooxirene; dimethylene oxide; 1,2-epoxyethane; EO; ETO; ethene oxide; oxane; α,β-oxidoethane.
CAS-No.	75-21-8
Use category	Pesticide
Use	Ethylene oxide is a powerful alkylating agent. Its chemical reactivity makes it a widely used intermediate in the chemical industry and an effective pesticide. Ethylene oxide is reported for the following uses: **Industrial use:** Virtually all ethylene oxide produced is used as an intermediate in the production of various chemicals, including ethoxylates, ethylene glycol, ethanol-amines, glycol-ethers, di-, tri- and polyethylene glycols and polyethylene terephthalate polyester. Certain of these chemicals are used in the production of surfactants, antifreeze and plastics for fibres, films and packaging materials. **Sterilant use:** A small fraction of the total production of ethylene oxide, alone or in combination with other inert gases such as carbon dioxide and nitrogen, is used to sterilize instruments from the health care, publication and wood product sectors. Ethylene oxide is used in other industries where heat sensitive goods are sterilized (*BUA, 1993*). **Pesticide use:** A small fraction of the total production of ethylene oxide is also used to control insects and microorganisms in fumigation of herbs and spices and for the control of wool and fur pests. Limited uses are also reported for treatment of empty food storage areas, food processing, preserving plants and shearing sheds. Previous uses were largely limited to fumigation of stored products and storage facilities. In Canada in 1996, 95 % of production was used in the manufacture of ethylene glycol. An estimated 4 % was used in the manufacture of surfactants. In the US in 1976, about 1% was used as an antimicrobial sterilant or as an insecticidal fumigant with less than 0.02% (500000 kg) of the production used for sterilization in hospitals (*Glaser, 1979; WHO, 1978)*). In Belgium, an estimated 0.07% of the total consumption of ethylene oxide (120000 kg) in 1980 was used in the health care and medical products industries *(Wolfs et al., 1983)*.
Trade names	Anprolene; Melgas; Merpal; SterigasP (pure products); Carboxide; Cartox; Etox; Oxyfume 20; 30; Sterigas 90/10; Steroxide 20; T-gas (formulations with carbon dioxide); Oxyfume 12; Sterigas 12/88; Steroxide 12/88 (formulations with fluorocarbons); Etoxiat; Amprolene; Anproline.
Formulation types	Liquified gas.
Basic manufacturers	Belco Resources, Inc.

Reasons for inclusion in the PIC procedure

Ethylene oxide is included in the PIC procedure based on reported bans and severe restrictions on its use as an agricultural pesticide. No control actions have been reported relating to its sterilant or industrial uses. Inclusion was recommended at the eighth meeting of the FAO/UNEP Joint Group of Experts on Prior Informed Consent.

Summary of control actions (see Annex 2 for details)

Control actions have been reported by 7 countries and the European Union. In 6 countries (Austria, Belize, Germany, Slovenia, Sweden, United Kingdom) ethylene oxide was reported as banned for pesticide use. China reported that its use as a pesticide has been restricted to the fumigation of empty storehouses, containers and cabins. In the European Union, pesticidal use for the control of wool and fur pests and industrial uses are still allowed. Concern about the effects of the substance on human health, especially addressing carcinogenicity, is reported as the reason for the control actions by most countries.

Hazard classification by organization

WHO	Gaseous or volatile fumigant not classified under the WHO recommended classification of pesticides by hazard (*IPCS , 1998-1999*)
EPA	Group B1 (probable human carcinogen). (*USEPA, 1998*)
EU	Toxic; carcinogen, cat. 2; mutagen, cat.. 2 (classification in accordance with Directive 67/548/EEC on the approximation of the laws, regulations and administrative provisions relating to the classification, packaging and labelling of dangerous substances, 12th ATP, 1991)
IARC	Group 1 (carcinogenic to humans). (*IARC, 1994*)

Protective measures that have been applied concerning the chemical

Measures to reduce exposure

Workplace controls are considered preferable to personal protective equipment. For some work, however, (such as outside work, confined space entry, work done only sporadically, or work done while workplace controls are being installed), personal protective equipment may be appropriate.

The following recommendations are only guidelines and may not apply to every situation:

Avoid skin contact with ethylene oxide. Wear protective gloves and clothing. Safety equipment suppliers/manufacturers can provide recommendations on the most suitable protective glove/clothing material for your operation.

All protective clothing (suits, gloves, footwear, headgear) should be clean, available each day, and put on before work. Hoechst Celanese *et al.* (1995) recommend chlorinated polyethylene, a synthetic rubber, as a protective material. Improper use of respirators is dangerous. Such equipment should only be used if the employer has a written programme that takes into account workplace conditions, requirements for worker training, respirator fit testing and medical exams. At any exposure level, use an approved supplied-air respirator with a full facepiece operated in the positive pressure mode or with a full facepiece, hood or helmet in the continuous flow mode, or use an approved self-contained breathing apparatus with

a full facepiece operated in pressure-demand or other positive pressure mode.

Proper personal protective equipment should be used whenever there is a potential for ethylene oxide exposure. Protective clothing should be suitable for ethylene oxide service. Many glove and suit materials are permeated by ethylene oxide and do not provide adequate protection. Even dilute solutions of ethylene oxide can cause severe chemical burns.

Exposure to 800 ppm is immediately dangerous to life and health. If the possibility of exposure above 800 ppm exists, use an approved self-contained breathing apparatus with a full facepiece operated in continuous flow or other positive pressure mode *(New Jersey Department of Health and Senior Services, 1994).*

Spilled ethylene oxide should either be allowed to evaporate or be diluted with water 22:1 in an open area and 100:1 in closed area to eliminate a fire hazard.

Ethylene oxide is heavier than air and can travel across the ground and reach a remote source of ignition causing a flashback fire danger. Dangerous polymerisation can occur on contact with highly catalytic surfaces.

Packaging and labelling

Follow the *FAO Revised Guidelines on Good Labelling Practice for Pesticides (1995)*.

The United Nations Committee of Experts on the Transportation of Dangerous Goods classifies the chemical in:

Hazard class 2.3

Packing: Prevent contamination of packing material. Ethylene oxide can react violently with metals such as copper, silver, magnesium and their alloys, acids, organic bases, ammonia and many other materials.

Protect containers against physical damage, check for leakage intermittently. Store in distant outdoor tank or container protected from direct sunlight, lined with insulating material, equipped with an adequate refrigeration and water system. Indoor storage should be restricted to small quantities. Place material in a combustible liquid cabinet which is fireproof in conformity with regulations *(ITII, 1988).*

Alternatives

No alternatives were reported by notifying countries.

Alternatives for stored products include chemical fumigants (aluminium phosphide, sulphur dioxide), inert gases such as carbon dioxide, irradiation, heat and cold treatment.

It is essential that before a country considers substituting any reported alternatives, it ensures that the use is relevant to its national needs.

Waste disposal

Waste should be disposed of in accordance with the provisions of the Basel Convention on the Control of Transboundary Movements of Hazardous Wastes and Their Disposal, any guidelines thereunder (*SBC, 1994*) and any other relevant regional agreements.

See the *FAO Guidelines on Prevention of Accumulation of Obsolete Pesticide Stocks (1995**),*** and *The Pesticide Storage and Stock Control Manual* (1996).

Wear protective clothing and respiratory equipment suitable for hazardous materials.

Ethylene oxide is highly flammable. Incineration is not an option. Ethylene oxide disposal should only be handled by someone with appropriate knowledge of ethylene oxide properties.

It should be noted that the methods recommended in literature are often not suitable in a specific country. Consideration should be given to the use of alternative destruction technologies.

Exposure limits

	Type of limit	Value
Food	MRLs (Maximum Residue Limits in mg/kg) in specified products (*FAO/WHO 1969*).	No MRLs allocated.
	JMPR ADI (Acceptable Daily Intake) in mg/kg diet (*FAO/WHO 1969*).	No ADI allocated.
Workplace	USA (Occupational Safety and Health Agency)	
	8 hour TWA (permissable exposure limit)	1 ppm PEL
	15 minute short-term exposure limit	5 ppm STEL
	USA TLV-TWA (Threshold Limit Value, Time-Weighted Average) (*ACGIH, 1999*).	1 ppm (1.8mg/m^3)

First aid

First aid: Move victim to fresh air. Call emergency medical care. Apply artificial respiration if victim is not breathing. Do not use mouth-to-mouth method if victim ingested or inhaled the substance; induce artificial respiration with the aid of a pocket mask equipped with a one-way valve or other proper respiratory medical device. Administer oxygen if breathing is difficult. Remove and isolate contaminated clothing and shoes. In case of contact with substance, immediately flush skin or eyes with running water for at least 20 minutes. In case of contact with liquefied gas, thaw frosted parts with lukewarm water. Keep victim warm and quiet. Keep victim under observation. Effects of contact or inhalation may be delayed. Ensure that medical personnel are aware of the material(s) involved, and take precautions to protect themselves. (*U.S. Department of Transportation, 1996*).

Annexes

Annex 1 – Further information on the substance

1 Chemical and physical properties

1.1	**Identity**	Ethylene oxide is a colourless, flammable gas.
1.2	**Formula**	C_2H_4O
	Chemical name	Oxirane (CA)
	Chemical type	Epoxide
1.3	**Solubility**	Miscible with water and most organic solvents.
	logP_{ow}	-0.30 *(Hansch and Leo, 1995)*
1.4	**Vapour pressure**	146 kPa at 20°C *(WHO, 1985)*
1.5	**Melting point**	-111 °C *(Budavari, 1989)*
1.6	**Boiling point**	11 °C
1.7	**Flammability**	Flammability in air is from >3% volume. The flash point is -20°C.
1.8	**Reactivity**	It is a highly reactive chemical.

2 Toxicity

2.1 General

2.1.1 **Mode of action**

Ethylene oxide forms macromolecular adducts with proteins and nucleic acids. Targets in proteins are the amino acids cysteine, histidine and valine (if N-terminal, as in hemoglobin). The major DNA adduct is 7-(2-hydroxyethyl)-guanine *(Bolt et al., 1988)*. Ethylene oxide is electrophilic and has direct alkylating effect on proteins and nucleic acids. It disperses rapidly and relatively uniformly in the organism. Consequently, all tissue can be reached in theory and thus be exposed to the alkylating properties of ethylene oxide. The fact that gamete-producing cells are also exposed has been demostrated *(BUA, 1993).*

2.1.2 **Uptake**

In mice inhalation studies ethylene oxide has been demonstrated to be very soluble in blood. Pulmonary uptake is expected to be fast and to depend only on the alveolar ventilation rate and the concentration of ethylene oxide in the inspired air *(Ehrenberg et al., 1974)*. Ethylene oxide is readily absorbed by oral, dermal and inhalatory routes and distributes itself in all tissues via the blood stream *(BUA, 1993).*

2.1.3 **Metabolism**

Available animal data indicate two possible pathways for the metabolism of ethylene oxide, i.e., hydrolysis and glutathione conjugation. Within 24 hours, 7-24% of the dose applied to dogs was excreted in the urine as 1,2-ethanediol (*Martis et al., 1982 in WHO, 1985)*.

In the serum of 18 workers occupationally exposed to ethylene oxide, the blood concentration of 1,2-ethanediol was found to be elevated compared with that in unexposed controls *(Wolfs et al., 1983)*.

The results of studies on rats, rabbits and monkeys have shown that some

1,2-ethanediol is metabolized but that most is excreted unchanged in the urine *(Gessner et al., 1961; McChessney et al., 1971 in WHO, 1985)*.

2.2 Known effects on human health

2.2.1 Acute toxicity

Symptoms of poisoning

Respiratory tract irritation was reported as hoarseness *(Thiess, 1963)* and coughing in 5 cases after acute accidental exposure to ethylene oxide vapour *(Metz, 1939 in WHO, 1985)*.

Acute effects on the nervous system in nearly all inhalation cases were marked by nausea, recurrent vomiting and headache. Less frequently reported effects included decreased consciousness (one case of coma), over-excitement, sleeplessness, muscular weakness, diarrhoea, and abdominal discomfort *(Blackwood and Erskine, 1938, Metz, 1939, Capellini and Ghezzi, 1965 in WHO, 1985; Thiess, 1963)*. Accidental skin exposure resulted in effects on the nervous system, such as nausea and repeated vomiting *(Sexton and Henson, 1949).* Accidental exposure of the eyes to the vapour of ethylene oxide can lead to conjunctivitis *(Thiess, 1963; Joyner, 1964).* Exposure of 12 men via a leaking sterilizer resulted in neurological disorders *(Gross et al., 1979, Jay et al., 1982 in WHO, 1985).*

2.2.2 Short and long-term exposure

In 4 young men exposed intermittently for 2 - 8 weeks to ethylene oxide (because of a leaking sterilizer) at levels of approximately 1000 mg/m^3, reversible peripheral neuropathy showing abnormal nerve conduction, headache, weakness and decreased reflexes in the extremities, lack of coordination, and a wide-based gait and a reversible acute encephalopathy with headache, nausea, vomiting, lethargy, recurrent motor seizures, agitation and a diffusely slow electroencephalogram were observed *(Gross et al., 1979 in WHO, 1985)*.

Polyneuropathy was also reported in 3 sterilizer operators *(Kuzuhara et al., 1983 in WHO, 1985)*.

In a study from the USSR it was reported that pregnancy toxaemia in the latter half of pregnancy and other complications were higher in operators (14.7%) exposed to a maximum concentration level of 1 mg/m^3 and laboratory workers (9.9%) than in administrative staff (4.6%) and outside controls (8%). However, the primiparae among the operators lost less blood perinatally than those in the other groups. Spontaneous abortion occurred in 10.5% of operators, 7.9% of laboratory workers and in 7.7% of administrative staff. Findings in this study do not indicate any unequivocal adverse effect of ethylene oxide exposure at these concentrations on the outcome of pregnancy *(Yakubova et al., 1976).*

An increase in chromosomal aberrations was found in the lymphocytes of workers sterilizing medical equipment in hospitals or factories *(Abrahams, 1980; Pero et al., 1981; Högstedt et al., 1983).* A 50% increase in aberration rate was found in workers exposed to ethylene oxide for 0.5-8 years. The mean number of micronuclei in the bone marrow cells of 64% of these workers was 3 times higher than in the controls *(Högstedt et al., 1983).*

A statistically significant correlation was found between sister chromatid exchange frequency and the level of ethylene oxide, as well as a multiple correlation between sister chromatid exchange frequency and ethylene oxide

exposure, smoking and age *(Sarto et al., 1984).* In the USA, the sister chromatid exchange frequencies in the lymphocytes of 61 sterilization workers involved in sterilizing health-care products, were monitored over a period of 2 years and compared with those of 82 unexposed controls. During the study period, 8-hour Time-Weighted-Average (TWA) exposure was reported to be less than 1.8 mg/m^3. Prior to the start of the study, 8-hours TWA ranged between 0.9 and 36 mg/m^3. In the USA, workers exposed to low levels of ethylene oxide, such as those at a worksite with 8-h time-weighted-average ethylene oxide levels below 1.8 mg/m^3 prior to and during the study, did not show increased frequencies of sister chromatid exchange. Workers who had been exposed to levels of 5-36 mg/m^3 prior to the study showed an increased frequency of sister chromatid exchange; results were adjusted for smoking habits, sex and age *(Stolley et al., 1984).*

Samples of blood were collected from a group of plant workers engaged in the manufacture of ethylene oxide for periods of up to 14 years, and also from a group of control personnel matched by age and smoking habits. Peripheral blood lymphocytes were cultured for cytogenetic analysis. Selected immune and hematological parameters were also investigated. The results of these studies showed no statistically significant difference between the group of plant workers and the control group in respect to any of the biological parameters investigated in this study. Nevertheless, duration of employment in ethylene oxide manufacturing was positively correlated ($p< 0.05$) with the frequency of chromosome breaks and with the percentage of neutrophils in a differential white blood cell count, and negatively correlated ($p< 0.05$) with the percentage of lymphocytes. As the values of these parameters remained within the normal limits of control populations, the correlations were considered to have no significance for health. *(Van Sittert et al., 1985).*

A study was made of the effects of ethylene oxide on the health of sterilizer workers and other personnel exposed while using ethylene oxide for sterilization of disposable medical devices. The only significant findings were obtained by chromosomal analysis of cultured lymphocytes harvested from the workers. There were significant differences in the numbers and types of chromosomal aberrations between the exposed workers and the nonexposed controls *(Richmond et al., 1985).*

The sister chromatid exchange rate in lymphocytes was not increased in groups of 28 and 14 sterilization workers exposed to 8-hour time-weighted averages below 1.8 mg/m^3 for 2.5 years before the study *(Högstedt et al., 1983)* and below 8 mg/m^3 *(Hansen et al., 1984),* respectively. Increases in sister chromatid exchange rate were found in 4 other studies on sterilization workers *(Garry et al., 1979, Abrahams, 1980, Yager and Benz, 1983, Laurent et al., 1984 in WHO, 1985).* In a study on 41 sterilization workers in 8 hospitals in Italy, increases in both sister chromatid exchanges and in chromosomal aberrations were detected in lymphocytes of workers exposed to 8-hour time-weighted averages of either 0.63 mg/m^3 or 19.3 mg/m^3 (Sarto *et al.*, 1984).

DNA repair inhibition was positively correlated with duration of exposure *(Pero et al., 1981).* In 7.1% male workers, an increase in chromosomal aberration rate was found that was significant for the workers exposed for more than 20 years, but not for those accidentally exposed or exposed for average periods of 12 to 17 years *(Thiess et al., 1981).*

2.2.3 **Epidemio-logical studies**

In a Swedish study on ethylene oxide exposure *(Högstedt et al., 1979a)* two cases of leukaemia appeared among 68 females working in a small factory sterilizing hospital equipment with a mixture of ethylene oxide and methyl formate. A third case of 1 male was attributed to the possible exposure to other carcinogens (e.g. benzene). The concentration of ethylene was in the range of 3.6-128 mg/m^3, and the 8-hour time-weighted average in the breathing zone was calculated to be between 36 ± 18 mg/m^3.

A second Swedish study to investigate the carcinogenic effects of ethylene oxide was conducted on 241 male workers in an ethylene oxide-producing plant. Twenty-three deaths occurred during the 16-year observation period dating from 1961–1977 (13.5 expected). The excess mortality was due to cancer and cardiovascular disease. Three cases of stomach cancer (0.4 expected) and 2 cases of leukaemia (0.14 expected) accounted for the excess mortality from cancer. No increase in mortality was observed among 66 unexposed controls. Average exposure levels were estimated to be below 25 mg/m^3 *(Högstedt et al., 1979b).*

The ethylene oxide was manufactured by the chlorohydrin process so that significant exposure to other chemicals such as 1,2-dichloroethane, ethylene, ethylene-chlorohydrin and bis(2-chloroethyl) ether might have occurred. This investigation was followed up by a study that extended the period of observation up to 1982. During the 20-year period of observation, a total of 17 cases of cancer were notified to the Cancer Registry against 7.9 expected *(Högstedt et al., 1984 in WHO, 1985).*

In a similar study in the USA, 767 male workers were exposed to ethylene oxide in a producing plant. Concentrations of ethylene oxide were reported to be below 18 mg/m^3. There were 46 deaths against 80 expected deaths *(IARC, 1994).*

Workers who had been employed for more than one year by a company producing ethylene oxide had been studied from 1960-1961. No significant differences had been found between workers permanently working in the ethylene oxide manufacturing area, those who had previously worked in this area, those working there intermittently and a further group who had never worked in ethylene oxide production. However, a subgroup of individuals with high exposure had decreased hemoglobin concentrations and signficant lymphocytosis. When workers were followed up from 1961-1977, those who had been exposed full-time to ethylene oxide production showed a considerably excess mortality, this being mainly due to an increased incidence of leukemia, stomach cancer and diseases of the circulatory system. Although malignancies could not be linked to any particular chemical associated with ethylene oxide production it was considered that ethylene oxide and ethylene dichloride, possibly together with ethylene chlorohydrin or ethylene, were the causative agents *(Reynolds and Prasad, 1982).*

A multi-centre cohort study was carried out to study the possible association

between exposure to ethylene oxide and cancer mortality. The cohort consisted of 2658 men from eight chemical plants of six chemical companies in the Federal Republic of Germany who had been exposed to ethylene oxide for at least one year between 1928 and 1981. The number of subjects in the separate plants varied from 98 to 604. By the closing date of the study (31 December 1982) 268 had died, 68 from malignant neoplasms. For 63 employees who had left the plant (2.4%) the vital status remained unknown. The standardized mortality ratio for all causes of death was 0.87 and for all malignancies 0.97 compared with national rates. When local state rates were used the standardized mortality ratio were slightly lower. Two deaths from leukemia were observed compared with 2.35 expected standardized = 0.85. Standardized mortality ratios for carcinoma of the esophagus (2.0) and carcinoma of the stomach (1.38) were raised but not significantly. In one plant an internal "control group" was selected matched for age, sex, and date of entry into the factory and compared with the exposed group. In both groups a "healthy worker effect" was observed. The total mortality and mortality from malignant neoplasms was higher in the exposed than in the control group; the differences were not statistically significant. There were no deaths from leukemia in the exposed group and one in the control group *(Kiesselbach et al., 1990)*.

In the Federal Republic of Germany, 602 workers were investigated for mortality experience during the period 1928–1980. A subcohort of 351 workers was observed for more than 10 years. Control data came from a styrene plant and from national statistics. Exposure to ethylene oxide had normally remained below 9 mg/m3. No information concerning the use of personal protective equipment was given. The workers were also exposed to many other chemicals. Exposure episodes to ethylene oxide concentration above the background level were also observed. There were 56 deaths compared with 76.6 expected. Fourteen deaths from cancer against 16.6 expected. In the subcohort of 351 workers, there was a significant increase in mortality rate due to kidney disease (3 against 0.4 expected) *(Thiess et al., 1981).*

A retrospective cohort study was conducted to examine the mortality experience of 2174 men employed between 1940 and 1978 by a large chemical company and who had been assigned to a chemical production department that used or produced ethylene oxide. Comparisons were made with the general United States population, the regional population, and with a group of 26965 unexposed men from the same plants. Comparisons with general United States death rates showed fewer deaths than expected in the ethylene oxide group due to all causes and for total cancers. There was no statistically significant excess of deaths due to any cause. Seven deaths each due to leukemia and pancreatic cancer were observed with 3.0 and 4.1 deaths expected. Among the subcohort of men who worked where both average and peak exposure levels were probably highest, however, one death due to pancreatic cancer (0.9 expected) and no deaths due to leukemia were observed. Four of the seven who died from leukemia and six of the seven died from pancreatic cancer had been assigned to the chlorohydrin department where the potential for exposure to ethylene oxide is judged to have been low. The relative risk of death due to each disease was strongly

related to duration of assignments to that department. When men who worked in the chlorohydrin department were excluded, there was no evidence for an association of exposure to ethylene oxide with pancreatic cancer or leukemia. Together with the failure to show independent ethylene oxide associations, the chlorohydrin department results suggest that leukemia and pancreatic cancer may have been associated primarily with production of ethylene chlorohydrin or propylene chlorohydrin, or both. These results emphasize the importance of examining additional concurrent asynchronous exposure among human populations exposed to ethylene oxide *(Greenberg, 1990).*

A cohort study was carried out of mortality among 2876 men and women exposed to ethylene oxide during its manufacture and use in England and Wales. The study cohort included employees from three companies producing ethylene oxide and derivative compounds such as polyethylene glycols and ethoxylates, from one company that manufactured alkoxides from ethylene oxide and from eight hospitals with ethylene oxide sterilizing units. While industrial hygiene data were not available before 1977, since then the time weighted average exposure has been less than 5 ppm in almost all jobs and less than 1 ppm in many. Past exposure was probably somewhat higher. In contrast to other studies, no clear excess of leukemia was noted (three deaths occurred versus 2.09 expected), and no increase in the incidence of stomach cancer (five deaths occurred versus 5.95 expected) was observed. This lack of consistency with the results of earlier studies may be due to differences in exposure levels. Total cancer mortality was similar to that expected from national and local death rates from this disease. Small excesses were noted in some specific cancers, but their relevance to ethylene oxide exposure was doubtful. No excess of cardiovascular disease was found. While the results of this study did not exclude the possibility that ethylene oxide is a human carcinogen, they suggested that any risk of cancer from currently permitted occupational exposure is small *(Gardner, 1989).*

Mortality from cancer among workers exposed to ethylene oxide has been studied in 10 distinct cohorts that include about 29800 workers and 2540 deaths. The study presents a review and meta-analysis of these studies, primarily for leukemia, non-Hodgkin's lymphoma, stomach cancer, pancreatic cancer, and cancer of the brain and nervous system. The magnitude and consistency of the standardized mortality ratios (SMRs) were evaluated for the individual and combined studies, as well as trends by intensity or frequency of exposure, by duration of exposure, and by latency (time since first exposure). Exposure to other workplace chemicals were examined as possible confounder variables. Three small studies initially suggested an association between ethylene oxide and leukemia, but in seven subsequent studies the SMRs for leukemia have been much lower. For the combined studies the SMR = 1.06 (95% confidence interval (95% CI) 0.73-1.48). There was a slight suggestion of a trend by duration of exposure (p = 0-19) and a suggested increase with longer latency (p = 0.07), but there was no overall trend in risk of leukemia by intensity or frequency of exposure; nor did a cumulative exposure analysis in the largest study indicate a quantitative association. There was also an indication that in two studies with increased risks the workers had been exposed to other potential carcinogens. For non-

Hodgkin's lymphoma there was a suggestive risk overall (SMR = 1.35, 95% CI 0.93-1.90). Breakdowns by exposure intensity or frequency, exposure duration, or latency did not indicate an association, but a positive trend by cumulative exposure (p = 0.05) was seen in the largest study. There was a suggested increase in the overall SMR for stomach cancer (SMR = 1.28, 95% CI 0.98-1.65) (CI 0.73-2.26) when heterogeneity among the risk estimates was taken into account, but analyses by intensity or duration of exposure or cumulative exposure did not support a causal association for stomach cancer. The overall SMRs and exposure-response analyses did not indicate a risk from ethylene oxide for pancreatic cancer (SMR = 0.98), brain and nervous system cancer (SMR = 0.89), or total cancer (SMR = 0.94). Although the current data do not provide consistent and convincing evidence that ethylene oxide causes leukemia or non-Hodgkin's lymphoma, the issues are not resolved and await further studies of exposed populations *(Shore,1993).*

2.3 Toxicity studies with laboratory animals and *in vitro* systems

2.3.1 Acute toxicity

oral

The LD_{50} for ethylene oxide, administered orally and dissolved in water, were 330 mg/kg body weight for male rats and 280 and 365 mg/kg body weight for female and male mice, respectively *(Smyth et al., 1941, Woodard and Woodard, 1971 in WHO, 1985).*

1,2-ethanediol, a metabolite, is less toxic: LD_{50} for rat were above 10 000 mg/kg body weight, after oral administration, and 5210 mg/kg body weight, after intravenous administration *(Woodard and Woodard, 1971 in WHO, 1985*).

After oral administration to rats, the difference between 0.1% mortality (325 mg/kg) and 99.9% mortality (975 mg/kg) was approximately 650 mg/kg body weight *(Smyth et al., 1941 in WHO, 1985).*

Dermal

Thirty 8-week old female icr/ha swiss mice were painted thrice weekly on clipped dorsal skin with approximately 0.1 ml of 10% solution in acetone for life-time. Median survival time was 493 days; no skin tumors were observed. *(IARC, 1976)*.

Inhalation

After inhalation, the 4-hour LC_{50} were 1500 and 1730 mg/m^3 for mouse and dog, respectively, and 2630 mg/m^3 for rat *(Jacobson et al., 1956 in WHO, 1985).*

After inhalation for 4 hours, this difference was approximately 3000 mg/m^3, in mice, and approximately 5000 mg/m^3 in rats. No deaths occurred in dogs at 1280 mg/m^3 *(Jacobson et al., 1956 in WHO, 1985).* In another study, no guinea pigs died after inhalation of 450 mg ethylene oxide/m^3 air for 8 hours, but the majority died at 2400 mg/m^3 *(Waite et al., 1930 in WHO, 1985).* In the above mortality studies, the lungs and nervous system were the main targets in rodents and dogs. In dynamic inhalation exposure studies on guinea pigs *(Waite et al., 1930 in WHO, 1985),* rats, mice, and dogs *(Jacobson et al., 1956 in WHO, 1985),* nasal irritation was the first clinical effect. Dogs exhibited laboured breathing, vomited and suffered convulsions. Guinea pigs, exposed to an ethylene oxide concentration of 13 000 mg/m^3 for 2.5 hours, were found lying on their sides, quiet and unable to stand. Gross pathological changes were observed in animals that did not survive, including moderate

congestion in the lungs of dogs, minor patchy oedema in the lungs of rats, and congestion with oedema in the lungs of guinea pigs. In rats, moderate congestion with petecchial haemorrhage of the trachea was also observed. Lobular pneumonia and hyperaemia of the liver and kidneys were observed in guinea-pigs. Parenchymatous changes in the kidney of guinea pigs were seen at 2300 mg/m^3.

Irritation

Skin irritation with hyperaemia, oedema and scar formation was observed from application of pads of cotton, moistened with solutions of ethylene oxide, under a plastic cover on the shaved skin of rabbits *(Hollingsworth et al., 1956 in WHO, 1985).*

If large amounts of material are involved, evaporation may cause sufficient cooling to cause a lesion similar to frostbite *(Hine and Rowe 1981 in WHO, 1985).*

2.3.2 **Short-term exposure**

Inhalation exposure - Wistar rats, guinea pigs, rabbits and female rhesus monkeys were exposed to concentrations of ethylene oxide at different levels of exposure for 7 hours per day and 5 days per week. No adverse effects in guinea pigs, rabbits and monkeys at 90 and 200 mg/m^3, and in rats at 90 mg/m^3. Rats showed elevated mortality rates from 370 mg/m^3, rabbits from 640 mg/m^3, and all exposed animals died at 1510 mg/m^3. At 370 mg/m^3, adverse effects in lungs were observed. Even more severe lung injury was seen in rats at 640 mg/m^3 and the higher exposure. Gross respiratory tract irritation was apparent in all species at 1510 mg/m^3. Monkeys and rabbits exhibited paralysis of the hind legs at 370 mg/m^3 and rats at 640 mg/m^3. *(Hollingsworth et al., 1956 in WHO, 1985).*

No effects were observed in relation to survival, body weight, clinical signs, white blood cell count, serum clinical chemistry, urine analysis and histopathology in B6C3F1 mice of each sex exposed to concentrations of ethylene oxide at 0, 18, 86, 187, or 425 mg/m^3 for 6 hours per day and 5 days per week. The exposure lasted for 10 weeks for males and 11 weeks for females. At the highest exposure level, changes at terminal sacrifice included an increased relative liver weight in female mice, and a decreased testicular weight in males and a decreased relative spleen weight and haemoglobin concentration *(Snellings et al., 1984).*

No effects were observed on mortality rate, body weight, electrocardiogram, blood-calcium and -urea, icteric index and rectal temperature in groups of 3 male beagle dogs each exposed to concentrations of ethylene oxide of 180 and 530 mg/m^3 for 1-3 days. Anaemia was noted at both exposure levels. Effects on the respiratory and nervous systems were shown at 530 mg/m^3. Muscular atrophy was also observed *(Jacobson et al., 1956 in WHO, 1985).* No haematological changes were noted in groups of 3 male New Zealand rabbits exposed for 12 weeks to 0, 18, 90 or 450 mg/m^3 *(Yager and Benz, 1982).* The white cell count was depressed in Fischer rats exposed in groups of 3 or 4, for 3 days, 6 hours per day, to 90, 270, or 810 mg/m^3. *(Kligerman et al., 1983).*

In 12 male cynomolgus monkeys exposed to 0, 90 or 180 mg ethylene oxide/m^3 for 7 hours per day, 5 days per week, for 2 years the only treatment-related lesions found were in the *medulla oblongata* of the brain. Axonal dystrophy was found in the *nucleus gracilis*, primarily in the exposed groups.

Demyelination of the terminal axons of the *fasciculus gracilis* occurred in one monkey at each exposure level, but not in the controls *(Sprinz et al., 1982).* Paralysis of the hind limbs was observed in monkeys repeatedly exposed for up to 32 weeks to 370 mg/m^3 for 7 hours per day, 5 days per *week (Hollingsworth et al., 1956 in WHO, 1985).*

2.3.3 **Long-term exposure**

In a combined toxicity-carcinogenicity study, groups of 120 male and 120 female Fischer 344 rats were exposed to actual concentrations of ethylene oxide of 18 mg/m^3 (10 ppm), 58 mg/m^3 (32 ppm) and 173 mg/m^3 (96 ppm) for 6 hours per day, 5 days per week, over 25 months. Two control groups of animal per sex were used. The mortality rates of male and female rats increased significantly from the 22nd or 23rd month, at the highest exposure, with a trend towards an increase at a level of 58 mg/m^3. Body weights in both sexes were depressed at 173 mg/m^3, from the end of the first week onwards until the end of the study. At 58 mg/m^3, the body weights of female rats were decreased between week 10 and 80. In females, the relative liver weights were increased in the 18th month at 173 mg/m^3. Relative spleen weights were increased in rats that developed leukaemia. Haematological changes were found in rats at all doses, but mainly at the end of the study in animals exposed to 173 mg/m^3; these included an elevated leukocyte count in both sexes, and a depressed red blood cell count and haemoglobin value in females. Some of these rats had leukaemia. Non-neoplastic histopathological changes observed included an elevated frequency of focal fatty metamorphosis of the adrenal cortices in both sexes and bone marrow hyperplasia in females at 173 mg/m^3. Mild skeletal muscular atrophy was observed after 2 years of exposure to 173 mg/*m^3 (Snellings et al., 1984)*.

In another toxicity-carcinogenicity study *(Lynch et al., 1984 in WHO, 1985),* groups of 80 male Fischer 344 rats were exposed to concentrations of ethylene oxide of 92 mg/m^3 (51 ppm) and 182 mg/m^3 (101 ppm) for 7 hours per day, 5 days per week, over 2 years. Eighty rats in the control group. The mortality rate increased at both exposure levels, the increase being significant at 182 mg/m^3. Only 19% of the rats survived 2 years of exposure at 182 mg/m^3 compared with 49% in the unexposed group. Body weights were reduced from the 3rd or 4th month onwards. The relative weights of adrenals and brain were increased at both exposure levels. The relative weights of lung and kidney were increased at 92 mg/m^3. Serum aspartate aminotransferase activity was increased in rats exposed to 92 and 182 mg/m^3. No other changes were found in haematology or clinical chemistry. Non-neoplastic histopathological changes included an elevated incidence of vacuolization and hyperplasia or hypertrophy in the adrenals at both exposure levels, and of atrophy and degeneration of skeletal muscle fibres at 182 mg/m^3. There were also increased incidences of inflammatory lesions of the lungs, nasal cavities, trachea and internal ear at both exposure levels. Eye cataracts developed in 9 out of 78 rats at 182 mg/m^3, 3 out of 79 in the 92 mg/m^3 group and 2 out of 77 in the controls.

2.3.4 **Effects on reproduction**

Ethylene oxide was injected intravenously on several days during organogenesis in the mouse. Skeletal malformations occurred in foetuses whose mother received 150 mg/kg which produced maternal toxicity. Doses of 75 mg/kg caused no defects. Rats were exposed on days 6-15 of gestation for 6 hours daily to 10-100 ppm. At the highest dose, foetal growth retardation

occurred but there was no increase in congenital defects. *(Shepard, 1986).*

The offspring of DBA/2J male mice exposed to ethylene oxide by inhalation had an increased incidence of both dominant visible and electrophoretically detected mutations over that found in control populations. The progeny at risk were obtained from matings during the exposure period and were the products of germ cells that were exposed throughout the entire spermatogenic process. Apparently, male germ cells repeatedly exposed to ethylene oxide during spermatogenesis are susceptible to ethylene oxide induced transmissible damage *(Lewis et al, 1986).*

The effects of systemic toxicity including reproductive toxicity of ethylene oxide on female rats were studied. When Wistar female rats were exposed to 250 ppm of ethylene oxide for six hours per day, five days per week for ten weeks, they showed inhibition of body weight gain and paralysis of the hindelegs. Hematogological examination revealed macrocytic and normochromic anemia with high reticulocyte counts. The oestrus cycle of the exposed group was prolonged and the percentage of the di-oestrus stage increased. There was no atrophy in the ovary or the uterus. However, the activity of glutathione reductase in the ovary decreased by 18% and that of glutathione-S-transferase increased by 30%. These results indicate that ethylene oxide has a similar effect on both female and male rats and that the female reproductive system is also affected *(Mori et al, 1989).*

2.3.5 **Mutagenicity**

In a dose-response study, male mice were exposed to inhalation of ethylene oxide for 4 consecutive days. Mice were exposed for 6 hours per day to 300 ppm, 400 ppm, or 500 ppm ethylene oxide for a daily total of 1800, 2400, or 3000 ppm per hour, respectively. In the dose-rate study, mice were given a total exposure of 1800 ppm per hour per day delivered either at 300 ppm in 6 hours, 600 ppm in 3 hours, or 1200 ppm in 1.5 hours. Quantitation of dominant-lethal responses was made on matings involving sperm exposed as late spermatids and early spermatozoa, the stages most sensitive to ethylene oxide. In the dose-response study, a dose-related increase in dominant-lethal mutations were observed, the dose-response curve proved to be nonlinear. In the dose-rate study, increasing the exposure concentrations resulted in increased dominant-lethal responses. *(Gosslee, 1986)*.

Earlier studies revealed that ethylene oxide or ethyl methanesulfonate induced high frequencies of midgestation and late foetal deaths and of malformations among some of the surviving foetuses when female mice were exposed at the time of fertilization of their eggs or during the early pronuclear stage of the zygote. Effects of the two mutagens are virtually identical. Thus in investigating the mechanisms responsible for the dramatic effects in the early pronuclear zygotes, the two compounds were used interchangeably in the experiments. First a reciprocal zygote-transfer study was conducted in order to determine whether the effect is directly on the zygotes or indirectly through maternal toxicity. And second cytogenetic analyses of pronuclear metaphases early cleavage embryos and midgestation foetuses were carried out. The zygote transplantation experiment rules out maternal toxicity as a factor in the foetal maldevelopment. Together with the strict stage specifically observed in the earlier studies this result points to a genetic cause for the abnormalities. However the cytogenetic studies failed to show structural or numerical chromosome aberrations. Since intragenic base changes and

deletions may also be ruled out it appears that the lesions in question induced in zygotes by the two mutagens are different from conventional ones and therefore could be a novel one in experimental mammalian mutagenesis. *(Katoh et al., 1989)*.

Ethylene oxide is a classical mutagen and a carcinogen based on evidence from studies in experimental animals. Chinese hamster V79 cells were treated for 2 hours with gaseous ethylene oxide, in sealed treatment chambers, and assayed for survival and mutagenic response by analysis of induced resistance to 6-thioguanine or ouabain. Significant numbers of mutants were produced at both genetic markers by 1250 - 7500 ppm ethylene oxide. Similarly, primary Syrian hamster embryo cells were treated for 2 or 20 hours with gaseous ethylene oxide in sealed treatment chambers and subsequently assayed for survival and increased sensitivity to SA7 virus transformation. Treatment concentrations extended from toxic to several non-toxic concentrations. After 2 hours ethylene oxide treatment at 625-2500 ppm a significant enhancement of virus transformation was observed. At 20 hours after treatment, no enhancement was observed. Treatment of hamster cells with ethylene oxide in both bioassay systems yielded concentration-related, quantitative results *(Hatch et al, 1986).*

2.3.6 **Carcinogenicity**

Various animal studies indicate a clear evidence of the carcinogenic effect of the substance *(IARC, 1976; NTP, 1987).*

Ethylene oxide was administered intragastrically by gavage at 2 dosages, 30 and 7.5 mg/kg body weight to groups of 50 female Sprague-Dawley rats twice weekly for a period of nearly 3 years using salad oil as the solvent. It induced local tumors, mainly squamous cell carcinomas of the forestomach, dependent on the dosage. The first tumor occurred in the 79th week. The following tumor rates resulted 62 and 16%. In addition carcinomata in situ, papillomas and reactive changes of the squamous epithelium of the forestomach were observed in other animals, but ethylene oxide did not induce tumors at sites away from the point of administration (*Dunkelberg, 1982).*

Groups of F344 rats of each sex were exposed to either ethylene oxide vapor (concentrations of 100, 33 or 10 ppm) or to room air 6 hours daily, 5 days per week, for up to 2 years. Three representative sections of the brain from each rat were evaluated. Of 23 primary brain tumors which were found, 2 were in control animals. Increased numbers of brain tumors were seen in 100 ppm and 33 ppm ethylene oxide exposed male and female rats. Significant trend analyses were found for both males and females, indicating that ethylene exposure > 10 ppm was related to the development of these brain tumors *(Garman et al., 1985).*

3 Exposure

3.1 **Food**

Levels in food up to 2420 mg/kg wet weight have been reported for 1,2-ethanediol and up to 65 mg/kg wet weight for 2,2'-oxybisethanol, 6-12 months after sterilization *(Scudamore and Heuser, 1971).* Food constituents can also be alkylated. Hydroxyethylated derivatives of amino acids, vitamins, alkaloids and sugars have been identified that might affect the nutritive value of food. A change in organoleptic properties has been reported for a variety of foodstuffs

(Oser and Hall, 1956; Gordon and Thornburg, 1959; Windmueller et al., 1959; Pfeilsticker and Siddiqui, 1976).

3.2 **Occupational**

In a total of 8 production plants, the levels of worker exposure to ethylene oxide in recent years were reported to be generally below 18 mg/m^3 *(Högstedt et al., 1979b; Morgan et al., 1981; Thiess et al., 1981).*

In the majority of samples, the concentration of ethylene oxide was less than 0.2 mg/m^3 while in the remaining samples, concentrations were of up to 11.6 mg/m^3 *(Van Sittert et al., 1985).* In a plant in the USA, typical average daily exposure were reported to be 0.3 - 4.0 mg/m^3 in 1979 *(Flores, 1983 in WHO, 1985).*

Thiess *et al.* (1981) reported an exposure of 3420 mg/m^3 during a plant breakdown.

In four hospital sterilization units in France, in 1980, concentrations between 0.9 and 410 mg/m^3 were measured after sampling for several minutes *(Mouilleseaux et al., 1983).*

Exposure after the opening of sterilizers, ranging from less than 0.2 to 111 mg/m^3, were found by personal sampling over several minutes in 16 hospitals in Belgium in 1981 - 83. In one other hospital, an average of 477 mg/m^3 was measured by personal sampling *(Lahaye et al., 1984).*

In six hospital sterilization units in Italy, using pure ethylene oxide, the 8-hour time-weighted average concentrations were 6.7 - 36 mg/m^3 with an average of 19.3 mg/m^3. Continuous sampling during the 5-min interval following the opening of sterilizers revealed time-weighted average concentrations of 112.5 mg/m^3. In two other hospitals in Italy, using 11% ethylene oxide in freon, the 8-hour time-weighted average level was 0.63 mg/m^3, and the 5-min exposure average level was 15.5 mg/m^3 *(Sarto et al., 1984).*

Time-weighted average exposure of Swedish personnel involved in sterilizing medical equipment in 1975 were 14 mg/m^3, when the sterilizer door was open, and 2.3 mg/m^3 when the door was closed *(Högstedt et al., 1983).*

Pero *et al*. (1981) reported 1-hour time-weighted average personal exposure of up to 18 mg/m^3 for a sterilization facility in Sweden.

For workers in sterilization rooms of a hospital in the USA, 15-min exposure of up to 86 mg/m^3 were found with 8-hour time-weighted averages ranging from less than 0.13 to 7.7 mg/m^3 and instantaneous peaks of up to 1430 mg/m^3 *(Hansen et al., 1984).*

Eight hour time-weighted averages of 0.9, 9 - 18, and 9 - 36 mg/m^3 were measured before the 1980s at 3 work-sites in the sterilization facilities of a plant manufacturing health-care products *(Stolley et al., 1984).*

3.3 **Environment**

No data are available concerning levels of ethylene oxide in air, water, or soil, following emission from production plants, and there are no data indicating that ethylene oxide occurs as a natural product. Most of the ethylene oxide used for fumigation or sterilization finally enters the environment, mainly in the air.

Uncontrolled emission of ethylene oxide from a hospital sterilization chamber led to high levels of the sterilant in the immediate surroundings. Concentrations of between 7700 and 12000 mg/m^3 were measured 2 – 3 meters from an exhaust pipe on the outside wall *(Dunkelberg and Hartmetz,*

1977).

3.4 **Accidental poisoning**

Ethylene oxide may also be absorbed by medical equipment during sterilization and may remain in the materials for some time, as the unchanged compound or as its reaction products. Factors affecting residue levels are similar to those mentioned in section 3.1 for food. Aeration and storage conditions are very important, particularly with respect to possible worker exposure.

4 Effects on the environment

4.1 Fate

The main pathway of entry of ethylene oxide into the environment is through its escape into the atmosphere due to evaporation and with vented gases during production, handling, storage, transport and use. Most of the ethylene oxide applied as a sterilant or fumigant will enter the atmosphere *(Bogyo et al., 1980).* In the USA, production losses were estimated at 13 kg per tonne of ethylene oxide produced by catalytic oxidation. Sterilization and fumigation processes were estimated to account for a loss of 9 kg per tonne of ethylene oxide produced or approximately 1% of the total consumption *(WHO, 1978).* In 1980, this would have meant a combined loss of 53 kilotonnes of ethylene oxide into the atmosphere in the USA, which is approximately 2% of the total production in the USA.

4.1.1 **Persistence**

At ambient levels, ethylene oxide will be removed from the atmosphere via oxidation by hydroxyl radicals. On the basis of a theoretical rate constant for this reaction, the atmospheric residence time of ethylene oxide was estimated to be 5.8 days *(Cupitt, 1980).* However, experimental data have shown the residence time to be 100-215 days, depending on the hydroxyl radical concentration and the ambient temperature (*USEPA, 1985).* Because of its high water solubility, ethylene oxide levels in air will also be reduced through washout by rain *(Conway et al., 1983)*.

The photochemical reactivity of ethylene oxide, in terms of its ozone-forming ability, is low *(Joshi et al., 1982).* Evaporation from water is a significant removal process. Under specific conditions, Conway *et al*. (1983) found a half-life of 1 hour for the evaporation of ethylene oxide from water. In the environment, chemical degradation in water through ionic reactions appears to be comparatively slow. In neutral, fresh water at 25 °C, ethylene oxide is broken down to form 1,2-ethanediol with a half-life of 14 days *(Conway et al., 1983).* At 0 °C, the half-life is 309 days. The reaction is acid- and base-catalysed *(Virtanen, 1963 in WHO, 1985).* In the presence of halide ions, 2-haloethanol will also be formed. In neutral water of 3% salinity, at 25 °C, 77% of ethylene oxide was found to react to form 1,2-ethanediol and 23% to form 2-chloroethanol with a half-life of 9 days *(Conway et al., 1983).*

4.1.2 **Bioconcentration**

Ethylene oxide is not expected to bioaccumulate.

4.2 Ecotoxicity

4.2.1 **Fish**

Fish are the most susceptible aquatic organisms. An LC_{50} of 90 mg/l was observed for goldfish exposed for 24 hours *(Bridie et al., 1979).*

4.2.2 **Aquatic invertebrates**

In *Daphnia magna* a 48h LC_{50} of 212 mg/l was observed *(Conway et al., 1983).*

4.2.3 **Birds** There are no studies on the effects of ethylene oxide on birds .

4.2.4 **Bees** There are no studies on the effects of ethylene oxide on bees.

Annex 2 - Details on reported control actions

AUSTRIA

Effective: 1992

Control action: All uses banned in agriculture.

Reasons: Carcinogenic and mutagenic properties.

Alternatives: Many alternatives for designated purposes.

BELIZE

Effective: 1985

Control action: The substance is banned for use in agriculture.

Uses still allowed: No remaining uses are allowed.

Reasons: Major fire and inhalation hazard.

CHINA

Effective: 1985

Control action: Ethylene oxide has been banned for registration, production and use as a pesticide. It has never been produced and used as a pesticide.

Uses still allowed: Ethylene oxide has been restricted for use in fumigating of empty storehouse, container and cabin only.

Reasons: Ethylene oxide is highly toxic. Its use will produce severely harmful effects to human health.

EUROPEAN UNION

Effective: 1991

Control action: It is prohibited to use or place on the market all plant protection products containing ethylene oxide as an active ingredient.

Uses still allowed: Pesticidal use for control of wool and fur pests and industrial uses are still allowed. Control of wool and fur pests is not covered by the plant protection legislation.

Reasons: The use of ethylene oxide for the fumigation of plants or plant products in storage leaves residues in foodstuffs which may give rise to harmful effects on human and animal health. Ethylene oxide has been classified by the European Community as a category 2 carcinogen (probably carcinogenic to humans). Ethylene oxide has also been classified by the European Community as a category 2 mutagen (probably mutagenic to humans).

(Member States of the European Union are: Austria, Belgium, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Luxembourg, Netherlands, Portugal, Spain, Sweden, United Kingdom.)

GERMANY

Effective: 1981

Control action: Totally banned for use as plant protection product.

Reasons: Highly toxic to warm blooded animals and man; suspected of having teratogenic effects; toxicologically critical residues in stored products (reaction with ingredients).

SLOVENIA

Effective: 1997

Control action: Banned for use in agriculture.

Reasons: This chemical was banned from the use in agriculture due to the effect of its toxic properties to human health and the environment according to the opinion given by the Commission on Poisons.

SWEDEN

Effective: 1991

Control action: Banned for use as a pesticide

Uses still allowed: No remaining uses allowed.

Reasons: This substance was suspended due to its carcinogenic properties.

UNITED KINGDOM

Effective: 1990

Control action: All uses revoked for agriculture under the Control of Pesticides Regulations.

Uses still allowed: No remaining uses allowed.

Reasons: Action taken due to evidence of carcinogenicity.

Annex 3 – List of designated national authorities

AUSTRIA

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BELIZE

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GERMANY

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CP **DNA** Industrial Chemicals and Pesticides

P **DNA** Pesticides

C **DNA** Industrial Chemicals

Annex 4 – References

ABRAHAMS, R.H. (1980). Recent studies with workers exposed to ethylene oxide. In: Jorkasky, J.F., ed. Safe use of ethylene oxide. Proceedings of the Educational Seminar, Washington DC, Health Industries Manufacturers Association, pp. 27-38, 211-220 (HIMA Report No. 80-4).

AMERICAN CONFERENCE OF GOVERNMENTAL INDUSTRIAL HYGIENISTS (ACGIH) (1999). Guide to Occupational Exposure Values. Cincinnati, OH: Publication Office ACGIH.

BOGYO, S. *et al*. (1980). Investigation of selected potential environmental contaminants: epoxides, Syracuse, New York, Center for Chemical Hazard Assessment, Syracuse Research Corporation (Report prepared for US EPA) (Report No. EPA 560/11-80-005, PB 80-183197).

BOLT, H.M. *et al.* (1988). *Internaltional Archive on Occupational Environmental Health* 60 (3): 141-4.

BRIDIE, A.L. *et al*. (1979). The acute toxicity of some petrochemicals to goldfish. Water Res., 13: 623-626.

BUA (1993). GDCh-Advisory Committee on Existing Chemicals of Environmental Relevance (BUA). Ethylene oxide. BUA Report 141.

BUDAVARI, S. (ed.) (1989). Merck Index - Encyclopedia of Chemicals, Drugs and Biologicals. Rahway, NJ: Merck and Co., Inc., p. 559.

CONWAY, R.A. *et al.* (1983). Environmental fate and effects of ethylene oxide. *Environmental Science and Technology*., 17: 107-112.

CUPITT, L.T. (1980). Fate of toxic and hazardous materials in the air environment, Research Triangle Park, North Carolina, US Environmental Protection Agency, Environmental Sciences Laboratory, Office of Research and Development (EPA No. 600/3-80-084, PB 80-221948).

DUNKELBERG, H. and HARTMETZ, G. (1977). Recording the air pollution by ethylene oxide in the region of clinical sterilization installations. *Zbl. Bakt. Hyg. (I. Abt. Orig. B)*, 164: 271-278 (in German).

DUNKELBERG, H. (1982). *British Journal of Cancer* 46 (6): 924-33.

EHRENBERG, L., *et al*. (1974). Evaluation of genetic risks of alkylating agents: tissue doses in the mouse from air contaminiated with ethylene oxide. *Mutation Research*, 24: 83-103.

FAO/WHO (1969). Pesticide residues in food - 1968. Report of the Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Expert Group on Pesticide Residues. FAO Plant Production and Protection Paper 78. Food and Agriculture Organization, Rome.

GARDNER, M.J. *et al.* (1989). *British Journal of Industrial Medicine.* 46 (12): 860-5.

GARMAN, R.H. *et al.* (1985). *Neurotoxicology* 6 (1): 117-38.

GLASER, Z.R. (1979). Ethylene oxide: toxicology review and field study results of hospital use. *Journal of Environmental and Pathological Toxicolology.,* 2: 173-208.

GORDON, H.T. and THORNBURG, W.W. (1959). Hydroxyethyl derivatives in prunes fumigated with 14C-ethylene oxide. *Journal of Agricultural and Food Chemistry,* 7: 196-200.

GOSSLEE, D.G. (1986). *Environmental Mutagenesis* 8 (1): 1-8.

GREENBERG H.L. *et al*. (1990). *British Journal of Industrial Medicine.* 47 (4): 221-30.

HANSEN, J.P. *et al*. (1984). Normal sister chromatid exchange levels in hospital sterilization employees exposed to ethylene oxide. *Journal of Occupupational Medicine*., 26: 29-32.

HANSCH, C., LEO, A. (1995). Exploring QSAR - Hydrophobic, Electronic, and Steric Constants. Washington, DC: American.

HATCH G.G. *et al*. (1986). *Environmental Mutagenesis* 8 (1): 67-76.

HOECHST CELANESE POLYESTER INTERMEDIATES, OCCIDENTAL CHEMICAL CORPORATION, SHELL CHEMICAL COMPANY and SUN COMPANY, INC. (1995). Ethylene Oxide User's Guide.

HÖGSTEDT, B. *et al*. (1983). Chromosome aberrations and micronuclei in bone marrow cells and peripheral blood lymphocytes in humans exposed to ethylene oxide. *Hereditas*, 98: 105-113.

HÖGSTEDT, C. et al. (1979a). Leukemia in workers exposed to ethylene oxide. *Journal of the American Medical Association*, 241 : 1132-1133.

HÖGSTEDT, C. *et al*. (1979b). A cohort study of mortality and cancer incidence in ethylene oxide production workers. *British Journal of industrial Medicine*., 26: 276-280.

IARC (1976). Monographs on the evaluation of the carcinogenic risk of chemicals to man. Geneva: World Health Organization, International Agency for Research on Cancer, V11 161 (1976) 1972-present.. V11 161.

IARC (1994). Monographs on the evaluation of the carcinogenic risk of chemicals to man. Geneva: World Health Organization, International Agency for Research on Cancer, V11 161 (1976) 1972-present. V60

IPCS (1998-1999). The WHO Recommended Classification of Pesticides by Hazard and Guidelines to Classification, International Programme on Chemical Safety 1998-1999, Table 7 p.37.

ITII (1988). The International Technical Information Institute. Toxic and Hazardous Industrial Chemicals Safety Manual. Tokyo, Japan, p. 237.

JOSHI, S.B. *et al*. (1982). Reactivities of selected organic compounds and contamination effects. *Atmospheric Environment*, 16: 1301-1310.

JOYNER, R.E. (1964). *Archives of Environmental Health.* 8:700-10.

KATOH, M. *et al*. (1989). *Mutation Research.* 210 (2): 337-44.

KIESSELBACH N. *et al.* (1990). *British Journal of Industrial Medicine*. 47 (3): 182-8.

KLIGERMAN, A.D. *et al*. (1983). Sister-chromatid exchange induction in peripheral blood lymphocytes of rats exposed to ethylene oxide by inhalation. *Mutation Research*., 120: 37-44.

LAHAYE, D. *et al*. (1984). Ethylene oxide levels in the sterilization units of hospitals. *Tijdschr. Soc. Gezondheidsz*., 62: 707-713 (in Dutch).

LEWIS S.E. *et al.* (1986). *Environmental Mutagenesis* 8 (6): 867-72.

MORGAN, R.W. *et al*. (1981). Mortality among ethylene oxide workers. *Journal of occupational Medicine*., 23: 767-770.

MORI K. *et al.* (1989). *Sangyo Ika Daigaku Zasshi* 11 (2): 173-9.

MOUILLESEAUX, A. *et al*. (1983). Teneurs atmosphériques en oxyde d'éthylène décelées dans l'environnement professionnel d'instalations de stérilisation ou de désinfection. *Archives des Maladies Professionnelles de Medecine du Travail et de Securite Sociale*, 44: 1-14.

NEW JERSEY DEPARTMENT OF HEALTH AND SENIOR SERVICES (1994). Hazardous Substance Fact Sheet: Ethylene Oxide. Revision of December 1994.

NTP. (1987). Technical Report Series No. 326 (1987) NIH Publication No. 88-2582 U.S. Department of Health and Human Services, National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC 27709.

OSER, B.L. and HALL, L.A. (1956). The effect of ethylene oxide treatment on the nutritive value of certain foods. *Food Technol.*, 10: 175-178.

PERO, E.W.*et al*. (1981). In vivo and in vitro ethylene oxide exposure of human lymphocytes assessed by chemical stimulation of unscheduled DNA synthesis. *Mutation Research*, 83: 271-289.

PFEILSTICKER, K. and SIDDIQUI, I.R. (1976). Isolation of the derivatives from cocoa-powder fumigated by ethylene oxide 1,2-14C and their structure suggested on the basis of I.R. and mass-spectrometry. *Z. Lebensm. Unters. Forsch*., 160: 19-27 (in German).

REYNOLDS, J.E.F., PRASAD, A.B. (eds.) (1982). Martindale-The Extra Pharmacopoeia. 28th ed. London: The Pharmaceutical Press. p. 562.

RICHMOND G.W. *et al*. (1985). *Archives of Environmental Health*. 40 (1): 20-25.

SARTO, F. *et al*. (1984). Cytogenetic damage in workers exposed to ethylene oxide. *Mutation Research*., 138: 185-195.

SBC (1994). Basel Convention on the Control of Transboundary Movements of Hazardous Wastes and Their Disposal, Secretariat of the Basel Convention, SBC No. 94/008.

SCUDAMORE, K.A. and HEUSER, S.G. (1971). Ethylene oxide and its persistent reaction products in wheat flour and other commodities: residues from fumigation or sterilization, and effects of processing. *Pesticides Science.,* 2: 80-91.

SEXTON, R.J. and HENSON, E.V. (1949). Dermatological injuries by ethylene oxide. *Journal of Industrial Hygiene and Toxicology,* 31: 297-300.

SHEPARD, T.H. (1986). Catalog of Teratogenic Agents. 5th ed. Baltimore, MD: The Johns Hopkins University Press, p. 246.

SHORE R. *et al.* (1993). *British Journal of Industria Medicine* 50 (11): 971-97

SNELLINGS, W.M. *et al*. (1984). A subchronic inhalation study on the toxicologic potential of ethylene oxide in B6C3F1 mice. *Toxicology and applied Pharmacology,* 76: 510-518.

SPRINZ, H. *et al*. (1982). Neuropathological evaluation of monkeys exposed to ethylene and propylene oxide, Kansas City, Missouri, Midwest Research Institute (Prepared for NIOSH) (PB 83-134817).

STOLLEY, P.D. *et al*. (1984). Sister-chromatid exchanges in association with occupational exposure to ethylene oxide. *Mutation Research*., 129: 89-102.

THIESS, A.M. (1963). Observation on the adverse health effects of ethylene oxide. *Archiv fur Toxikologie*, 20: 127-140 (in German).

THIESS, A.M. *et al*. (1981). Mutagenicity study of workers exposed to alkene oxides (ethylene oxide/propylene oxide) and derivatives. *Journal of occupational Medicine*., 23: 343-347.

U.S. DEPARTMENT OF TRANSPORTATION (1996). North American Emergency Response Guidebook. A Guidebook for First Responders During the Initial Phase of Hazardous Materials/Dangerous Goods Incident. U.S. Department of Transportation. Research and Special Programs Administration, Office of Hazardous Materials Initiatives and Training (DHM-50), Washington, D.C. (1996),p. G-119.

USEPA (1985). Health assessment document for ethylene oxide, Washington DC, US Environmental Protection Agency (EPA 600/8-84/009F). United States Environmental Protection Agency.

USEPA (1998). Factsheet on Ethylene oxide, http://www.epa.gov/ttnuatw1/hlthef/ethylene.html (May 26, 1998). United States Environmental Protection Agency.

VAN SITTERT N.J. *et al*. (1985). Cytogenetic, immunological, and haematological effects in workers in an ethylene oxide manufacturing plant. *British Journal of Industrial Medicine*. 42(1):19-26.

WHO (1978). Environmental health problems associated with the manufacture and uses of synthetic organic chemicals, Geneva, World Health Organization (Report No. HCS/78.2).

WHO (1985). Environmental Health Criteria Monographs Ethylene oxide (EHC 55, 1985).

WINDMUELLER, H.G. *et al*. (1959). Reaction of ethylene oxide with nicotinamide and nicotinic acid. *Journal of Bioogical. Chemistry*, 234: 889-894.

WOLFS, P. *et al*. (1983). Surveillance des travailleurs exposés a l'oxyde d'éthylène dans une enterprise de distribution de gaz stérilisants et dans des unités de stérilisation de matériel médical. *Archives des Maladies Professionnelles de Medecine du Travail et de Securite Sociale*, 44: 321-328.

YAGER, J.W. and BENZ, R.D. (1982). Sister-chromatid exchanges induced in rabbit lymphocytes by ethylene oxide after inhalation exposure. *Environental Mutagenesis*, 4: 121-134.

YAKUBOVA *et al*. (1976). Gynaecological disorders in workers engaged in ethylene oxide production. *Kazansky Mededical Zhurnal*, 57: 558-560 (in Russian).

Annex III

REPORT OF THE CONTACT GROUP ON CONTAMINANTS

Chairs: Karel Gijsbertsen, A. Abdelbagi
Rapporteur: Goede
Evening session 2000-02-23, Morning session 2000-02-24

Definitions:

Contaminant:
Any constituent other than active ingredient, including impurities, remaining starting materials and/or any degradation products of them, present or appearing at the production stage, or during storage, transport and use, being of health or environmental concern.

Avoidable / unavoidable / intentionally / unintentionally: The different concepts were discussed but it was not found useful to find a solution, for example:

- most contaminants are avoidable, either by changing the feedstock and/or manufacturing process, but it may be impractical due to for example cost issues.

Scenarios:
General assumption: Basic active ingredient is of no concern, only the contaminant has adverse effects.

Two notifications from two PIC-regions (ban or severe restriction) are required for consideration of the substance. Action taken for health or environment reasons, based on risk evaluation.

1) Two countries out of two PIC-regions take an action because of contaminant-
Consequence: no use permitted

2) Two countries out of two PIC-regions take an action on substances with more than e.g.(x) pm contaminant-
Consequence: substances with more than e.g.(x) ppm contaminants are prohibited.

a) Product specification applies to two countries only
b) Product specification applies on global scale
c) Country A takes an action on a substance X with contaminant Y, Country B takes an action on a substance X with contaminant Z – Consequence: substances are prohibited.

3) Several countries take action on the same contaminant with different level of contaminant (Product specification applies to more than two countries)

4) Restricted use only on certain crops or certain uses

Scenario 1)
Two notifications from two PIC-regions (ban or severe restriction) taken because of same contaminant(s)-Consequence: no use permitted

Solution:
The substance will be proposed for inclusion in the PIC procedure

Scenario 2.a)
Two countries out of two PIC-regions take an action on substances with more than e.g.(x)ppm contaminant – Consequence: substances with more than e.g.(x)ppm contaminants are prohibited.

- Product specification applies to two countries only

Solution:
- substance with more than e.g.(x)ppm contaminant to be suggested for PIC listing, a DGD developed
- specifying the contaminant name only, a DGD developed (seems to be more appropriate for industrial chemicals, risk assessment will be difficult
- FAO specification could offer solution where ever applied

Scenario 2.b)
Two countries out of two PIC-regions take an action on substances with more that e.g.(x)ppm contaminant – Consequence: substances with more than e.g.(x)ppm contaminants are prohibited.

- Product specification applies on global scale

Solution:
- FAO specification could offer solution when globally applied
- To be considered by ICRC, determine whether the problem presently exists, situation regarding the substance should regularly be reviewed, otherwise PIC listing will be considered again

Scenario 2.c)
Country A takes an action on a substance X with contaminant Y, Country B takes an action on a substance X with contaminant Z – Consequence: substances are prohibited

Solution:
- feed back in 2a) and 2b)

Scenario 3)
Several countries take action on the same contaminant with different level of contamination

Solution:
- name the contaminants in the title of the DGD, and provide specific details of individual levels of the contaminants in the DGD

Scenario 4)
Restricted use only on certain crops of certain uses

Solution: Article 14 of the Convention

Annex IV

PROPOSED PROCESS FOR DRAFTING DECISION GUIDANCE DOCUMENTS

A. Flow chart

When Secretariat has identified 2 verified notifications from 2 PIC regions

When Secretariat has verified that a proposal contains information required (Annex IV part 1) and has collected additional information (annex IV part 2)

1. Secretariat forwards the notifications/proposal and accompanying documentation to the ICRC experts

2. ICRC experts, by correspondence, provide comments on the accompanying documentation and an ICRC Task Group is established

3. The ICRC Task Group incorporates comments and presents the notifications at a full meeting of the ICRC. The experts decide to recommend the chemical and develop an internal proposal.

4. The internal proposal is then circulated to the ICRC and its observers (States, IGOs, NGOs) for information

5. ICRC Task Group incorporates comments and prepares a draft DGD

6. The draft DGD is distributed as a meeting document (in the six official languages of the United Nations) for discussion at an ICRC meeting for finalization and approval

7. The ICRC forwards the recommendation and draft DGD to the INC for decision.

B. Proposed process for drafting DGDs for banned and severely restricted chemicals

Once the format for a Decision Guidance Document is established, it would facilitate the task of the Secretariat to forward the notifications and accompanying documentation, based on the information contained in the notifications of final regulatory action (as per Annex I and II).

ICRC must deem a notification valid prior to developing a DGD. It is thus important that there be clear guidance as to what constitutes an acceptable/valid notification in order that the Secretariat could undertake to prepare the documentation mentioned above.

Where the information is deemed insufficient the Secretariat would be responsible to follow-up with the notifying party. The document would not be brought to the ICRC until the relevant information had been provided.

In situations where it is unclear the Secretariat would seek guidance from the ICRC.

(1)[*] Where the information in the notification was deemed sufficient, the Secretariat would forward the notifications and accompanying documentation to the experts of the ICRC **(2)** for an initial round of comment. An ICRC Task Group would be established. The Secretariat would collate the comments into a tabular format and forward them to the Task Group.

(3) The Task Group would incorporate comments, as appropriate, indicating those comments taken up and those which were not and why.

The Task Group would present the notifications and the accompanying documentation to the ICRC along with the tabular summary of comments. The ICRC will decide whether to make a recommendation to include the chemical in the PIC procedure, and develop an internal proposal for a DGD.

(4) The internal proposal (and the tabular summary of comments) is then circulated to the ICRC and its observers for information. Any comments would be directed to the Secretariat, who would prepare a tabular summary for the review by the Task Group.

(5) The Task Group would prepare a draft DGD.

(6) This draft DGD is distributed as a meeting document for discussion at an ICRC meeting (in 6 languages) for finalization and approval.

(7) The ICRC forwards the recommendation and draft DGD to the INC for decision. The final documentation forwarded by the Secretariat to all Parties and observers in advance of the INC would include the draft DGD, the ICRC recommendation for inclusion in the PIC procedure, a summary of the ICRC deliberations including a rationale based on the criteria listed in Annex II , as well as the tabular summary of comments received under step 4 and how they were addressed.

Regional coordination by members of the ICRC in preparing and providing comments is encouraged.

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[*] Numbers refer to steps in the flow chart.

C. Proposed process for drafting DGDs for severely hazardous pesticide formulations

Once the format for a Decision Guidance Document is established, it would facilitate the task of the Secretariat to forward the proposal and accompanying documentation, based on the information contained in the proposal and the additional information collected by the Secretariat in accordance with Annex IV Part 2.

ICRC must deem the proposal valid prior to developing a DGD. It is thus important that there be clear guidance as to what constitutes an acceptable/valid proposal in order that the Secretariat could undertake to prepare the documentation mentioned above.

Where the information is deemed insufficient the Secretariat would be responsible to follow-up with the proposing party. The document would not be brought to the ICRC until the relevant information had been provided.

In situations where it is unclear, the Secretariat would seek guidance from the ICRC.

(1) [*] Where the information in the proposal was deemed sufficient, the Secretariat would collect the information in Part 2 of Annex IV from designated national authorities and non-governmental organizations and forward the proposal and accompanying documentation to the experts of the ICRC **(2)** for an initial round of comment. An ICRC Task Group would be established. The Secretariat would collate the comments into a tabular format and forward them to the Task Group.

(3) The Task Group would incorporate comments, as appropriate, indicating those comments taken up and those which were not and why.

The Task Group would present the proposal and the accompanying documentation to the ICRC along with the tabular summary of comments. The ICRC will decide whether to make a recommendation to include the pesticide formulation in the PIC procedure, and develop an internal proposal for a DGD.

(4) The internal proposal (and the tabular summary of comments) is then circulated to the ICRC and its observers for information. Any comments would be directed to the Secretariat, who would prepare a tabular summary for the review by the Task Group.

(5) The Task Group would prepare a draft DGD.

(6) This draft DGD is distributed as a meeting document for discussion at an ICRC meeting (in 6 languages) for finalization and approval.

(7) The ICRC forwards the recommendation and draft DGD to the INC for decision. The final documentation forwarded by the Secretariat to all Parties and observers in advance of the INC would include the draft DGD, the ICRC recommendation for inclusion in the PIC procedure, a summary of the ICRC deliberations including a rationale based on the criteria listed in Annex II , as well as the tabular summary of comments received under step 4 and how they were addressed.

Regional coordination by members of the ICRC in preparing and providing comments is encouraged.

[*] Numbers refer to steps in the flow chart.

Annex V

WORK PLAN FOR DEVELOPING OPERATIONAL PROCEDURES FOR THE INTERIM CHEMICAL REVIEW COMMITTEE

Task Group No.	HIGH PRIORITY TASKS	ICRC members and observers participating in the Task Group	WHEN
1	Revise Notification Form, Article 5, to make it fully consistent with Annex I Revise guidance on providing information, linking the information to the criteria in Annex II	Secretariat (lead) Reiner Arndt Cathleen Barnes Marc Debois Karel Gijsbertsen Masayuki Ikeda	1/
2	Prepare form for Proposal under Article 6, based on Annex IV, part 1 Develop incident report form Develop guidance on providing information, linking the information to the criteria in Annex IV, part 3.	Bill Murray (lead) Azhari Omer Abdelbagi Mohamed Ammati Cathleen Barnes Mercedes Bolaños Granda Ian Coleman Marc Debois Mohamed El Zarka Masayuki Ikeda Tamás Kõmives Julio Monreal Fatoumata Jallow Ndoye Sandra de Souza Hacon Kasumbogo Untung Dudley Achu Sama Secretariat NGOs: GCPF (Jakob Brassel) IUF (Peter Hurst)	1/
3	A. Develop formats for DGDs for banned and severely restricted pesticides and industrial chemicals, based on format of notification which collected the information (Annex I and Annex IV) B. Develop formats for DGDs for severely hazardous pesticides formulations, based on format of notification which collected the information (Annex I and Annex IV)	Secretariat (lead) Reiner Arndt Cathleen Barnes Marc Debois Karel Gijsbertsen Masayuki Ikeda Dudley Achu Sama Secretariat (lead) Azhari Omer Abdelbagi Mohamed Ammati Cathleen Barnes Mercedes Bolaños Granda Ian Coleman Marc Debois Mohamed El Zarka Masayuki Ikeda Julio Monreal Bill Murray Fatoumata Jallow Ndoye Sandra de Souza Hacon Ravinandan Sibartie Kasumbogo Untung Dudley Achu Sama NGOs: GCPF (Jakob Brassel) IUF (Peter Hurst)	1/
4	Cooperation and coordination on notifications according to Article 5	Cathleen Barnes (lead) Reiner Arndt Marc Debois Karel Gijsbertsen Jan Ferdinand Goede	1/

1/ Deadline will depend on timing of next ICRC session. The product of the Task Group's work will need to be circulated minimum 6 weeks before the ICRC session takes place.

Annex VI

OBSERVATIONS BY REPRESENTATIVES OF NON-GOVERNMENTAL ORGANIZATIONS

A. Global Crop Protection Federation (GCPF)

1. The Global Crop Protection Federation (GCPF) accepts that, if a regulatory action is taken to ban or severely restrict a substance for health or environmental reasons because a contaminant of concern is present in the substance at an unacceptable level, this action would constitute one of the grounds for consideration of that substance as a candidate for inclusion in the PIC procedure. If, however, the contaminant is reduced to an acceptable level through improvements in the manufacturing process or other means, the substance would not qualify for consideration as a candidate.

2. GCPF considers that an FAO specification is an acceptable international standard for product quality. If a substance is included in the PIC procedure because of an unacceptable level of a contaminant of concern, the decision and the title of the decision guidance document should be, "substance (X) with impurity (Y) at levels greater than (Z) ppm." If the chemical with the contaminant of concern at an unacceptable level is no longer traded, the chemical should not be included in the procedure, because the criteria of the Convention will not be met.

B. Other organizations

3. A number of observers noted their regret at not having received invitations to attend the meeting.

Annex VII

LIST OF DOCUMENTS BEFORE THE COMMITTEE AT ITS FIRST SESSION

SYMBOL	TITLE
UNEP/FAO/PIC/ICRC.1/1	Provisional agenda
UNEP/FAO/PIC/ICRC.1/Add.1	Annotated provisional agenda
UNEP/FAO/PIC/ICRC.1/2	Review of the role and mandate of the Interim Chemical Review Committee
UNEP/FAO/PIC/ICRC.1/3	General presentation of the PIC procedure in the Convention
UNEP/FAO/PIC/ICRC.1/4	Consideration of draft decision guidance documents referred to the Interim Chemical Review Committee by the Intergovernmental Negotiating Committee for the following four chemicals: ethylene dichloride, ethylene oxide, maleic hydrazide and bromacil
UNEP/FAO/PIC/ICRC.1/Add.1	Draft decision guidance document on ethylene dichloride
UNEP/FAO/PIC/ICRC.1/Add.2	Draft decision guidance document on ethylene oxide
UNEP/FAO/PIC/ICRC.1/Add.3	Draft decision guidance document on maleic hydrazide
UNEP/FAO/PIC/ICRC.1/Add.4	Draft decision guidance document on bromacil
UNEP/FAO/PIC/ICRC.1/5	Review of operational procedures for the Interim Chemical Review Committee
UNEP/FAO/PIC/ICRC.1/INF/1	Rules of procedure of the Intergovernmental Negotiating Committee for an international legally binding instrument for the application of the prior informed consent procedure for certain hazardous chemicals and pesticides in international trade
UNEP/FAO/PIC/ICRC.1/INF/2 and Add.1	Compilation of notifications of control actions, background documents and comments on the draft decision guidance documents on ethylene dichloride, ethylene oxide, maleic hydrazide and bromacil
UNEP/FAO/PIC/ICRC.1/INF/3 and Add.1 and Add.2	Designation of experts for the Interim Chemical Review Committee

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