UNITED NATIONS ENVIRONMENT PROGRAMME
INTERNATIONAL LABOUR ORGANISATION
WORLD HEALTH ORGANIZATION

INTERNATIONAL PROGRAMME ON CHEMICAL SAFETY

Environmental Health Criteria 218

FLAME RETARDANTS: TRIS(2-BUTOXYETHYL) PHOSPHATE, TRIS(2-ETHYLHEXYL) PHOSPHATE AND TETRAKIS(HYDROXYMETHYL) PHOSPHONIUM SALTS

First draft prepared by Dr G.J. van Esch, Bilthoven, the Netherlands

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

The Inter-Organization Programme for the Sound Management of Chemicals (IOMC) was established in 1995 by UNEP, ILO, the Food and

Agriculture Organization of the United Nations, WHO, the United Nations Industrial Development Organization, the United Nations Institute for Training and Research, and the Organisation for Economic Co-operation and Development (Participating Organizations), following recommendations made by the 1992 UN Conference on Environment and Development to strengthen cooperation and increase coordination in the field of chemical safety. The purpose of the IOMC is to promote coordination of the policies and activities pursued by the Participating Organizations, jointly or separately, to achieve the sound management of chemicals in relation to human health and the environment.

WHO Library Cataloguing-in-Publication Data

Flame retardants : tris(2-butoxyethyl) phosphate, tris(2-ethylhexyl) phosphate, tetrakis(hydroxymethyl) phosphonium salts.

(Environmental health criteria ; 218)

1.Organophosphorus compounds - toxicity 2.Phosphoric acid esters - toxicity 3.Flame retardants - toxicity
4.No-observed-adverse-effect level 5.Environmental exposure
6.Occupational exposure I.Series

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NOTE TO READERS OF THE CRITERIA MONOGRAPHS

Every effort has been made to present information in the criteria monographs as accurately as possible without unduly delaying their publication. In the interest of all users of the Environmental Health Criteria monographs, readers are requested to communicate any errors that may have occurred to the Director of the International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland, in order that they may be included in corrigenda.

* * *

A detailed data profile and a legal file can be obtained from the International Register of Potentially Toxic Chemicals, Case postale 356, 1219 Châtelaine, Geneva, Switzerland (telephone no. + 41 22 - 9799111, fax no. + 41 22 - 7973460, E-mail irptc@unep.ch).

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Environmental Health Criteria

PREAMBLE

Objectives

In 1973 the WHO Environmental Health Criteria Programme was initiated with the following objectives:

(i) to assess information on the relationship between exposure to environmental pollutants and human health, and to provide guidelines for setting exposure limits;

(ii) to identify new or potential pollutants;

(iii) to identify gaps in knowledge concerning the health effects of pollutants;

(iv) to promote the harmonization of toxicological and epidemiological methods in order to have internationally comparable results.

The first Environmental Health Criteria (EHC) monograph, on mercury, was published in 1976 and since that time an ever-increasing number of assessments of chemicals and of physical effects have been produced. In addition, many EHC monographs have been devoted to evaluating toxicological methodology, e.g., for genetic, neurotoxic, teratogenic and nephrotoxic effects. Other publications have been concerned with epidemiological guidelines, evaluation of short-term tests for carcinogens, biomarkers, effects on the elderly and so forth.

Since its inauguration the EHC Programme has widened its scope, and the importance of environmental effects, in addition to health effects, has been increasingly emphasized in the total evaluation of chemicals.

The original impetus for the Programme came from World Health Assembly resolutions and the recommendations of the 1972 UN Conference on the Human Environment. Subsequently the work became an integral part of the International Programme on Chemical Safety (IPCS), a cooperative programme of UNEP, ILO and WHO. In this manner, with the strong support of the new partners, the importance of occupational health and environmental effects was fully recognized. The EHC monographs have become widely established, used and recognized throughout the world.

The recommendations of the 1992 UN Conference on Environment and Development and the subsequent establishment of the Intergovernmental Forum on Chemical Safety with the priorities for action in the six programme areas of Chapter 19, Agenda 21, all lend further weight to the need for EHC assessments of the risks of chemicals.

Scope

The criteria monographs are intended to provide critical reviews on the effect on human health and the environment of chemicals and of combinations of chemicals and physical and biological agents. As such, they include and review studies that are of direct relevance for

the evaluation. However, they do not describe *every* study carried out. Worldwide data are used and are quoted from original studies, not from abstracts or reviews. Both published and unpublished reports are considered and it is incumbent on the authors to assess all the articles cited in the references. Preference is always given to published data. Unpublished data are only used when relevant published data are absent or when they are pivotal to the risk assessment. A detailed policy statement is available that describes the procedures used for unpublished proprietary data so that this information can be used in the evaluation without compromising its confidential nature (WHO (1990) Revised Guidelines for the Preparation of Environmental Health Criteria Monographs. PCS/90.69, Geneva, World Health Organization).

In the evaluation of human health risks, sound human data, whenever available, are preferred to animal data. Animal and *in vitro* studies provide support and are used mainly to supply evidence missing from human studies. It is mandatory that research on human subjects is conducted in full accord with ethical principles, including the provisions of the Helsinki Declaration.

The EHC monographs are intended to assist national and international authorities in making risk assessments and subsequent risk management decisions. They represent a thorough evaluation of risks and are not, in any sense, recommendations for regulation or standard setting. These latter are the exclusive purview of national and regional governments.

Content

The layout of EHC monographs for chemicals is outlined below.

* Summary -- a review of the salient facts and the risk evaluation of the chemical
* Identity -- physical and chemical properties, analytical methods
* Sources of exposure
* Environmental transport, distribution and transformation
* Environmental levels and human exposure
* Kinetics and metabolism in laboratory animals and humans
* Effects on laboratory mammals and *in vitro* test systems
* Effects on humans
* Effects on other organisms in the laboratory and field
* Evaluation of human health risks and effects on the environment
* Conclusions and recommendations for protection of human health and the environment

* Further research
* Previous evaluations by international bodies, e.g., IARC, JECFA, JMPR

Selection of chemicals

Since the inception of the EHC Programme, the IPCS has organized meetings of scientists to establish lists of priority chemicals for subsequent evaluation. Such meetings have been held in: Ispra, Italy, 1980; Oxford, United Kingdom, 1984; Berlin, Germany, 1987; and North Carolina, USA, 1995. The selection of chemicals has been based on the following criteria: the existence of scientific evidence that the substance presents a hazard to human health and/or the environment; the possible use, persistence, accumulation or degradation of the substance shows that there may be significant human or environmental exposure; the size and nature of populations at risk (both human and other species) and risks for environment; international concern, i.e. the substance is of major interest to several countries; adequate data

on the hazards are available.

If an EHC monograph is proposed for a chemical not on the priority list, the IPCS Secretariat consults with the Cooperating Organizations and all the Participating Institutions before embarking on the preparation of the monograph.

Procedures

The order of procedures that result in the publication of an EHC monograph is shown in the flow chart. A designated staff member of IPCS, responsible for the scientific quality of the document, serves as Responsible Officer (RO). The IPCS Editor is responsible for layout and language. The first draft, prepared by consultants or, more usually, staff from an IPCS Participating Institution, is based initially on data provided from the International Register of Potentially Toxic Chemicals, and reference data bases such as Medline and Toxline.

The draft document, when received by the RO, may require an initial review by a small panel of experts to determine its scientific quality and objectivity. Once the RO finds the document acceptable as a first draft, it is distributed, in its unedited form, to well over 150 EHC contact points throughout the world who are asked to comment on its completeness and accuracy and, where necessary, provide additional material. The contact points, usually designated by governments, may be Participating Institutions, IPCS Focal Points, or individual scientists known for their particular expertise. Generally some four months are allowed before the comments are considered by the RO and author(s). A second draft incorporating comments received and approved by the Director, IPCS, is then distributed to Task Group members, who carry out the peer review, at least six weeks before their meeting.

The Task Group members serve as individual scientists, not as representatives of any organization, government or industry. Their function is to evaluate the accuracy, significance and relevance of the information in the document and to assess the health and environmental risks from exposure to the chemical. A summary and recommendations for further research and improved safety aspects are also required. The composition of the Task Group is dictated by the range of expertise required for the subject of the meeting and by the need for a balanced geographical distribution.

The three cooperating organizations of the IPCS recognize the important role played by nongovernmental organizations. Representatives from relevant national and international associations may be invited to join the Task Group as observers. While observers may provide a valuable contribution to the process, they can only speak at the invitation of the Chairperson. Observers do not participate in the final evaluation of the chemical; this is the sole responsibility of the Task Group members. When the Task Group considers it to be appropriate, it may meet *in camera*.

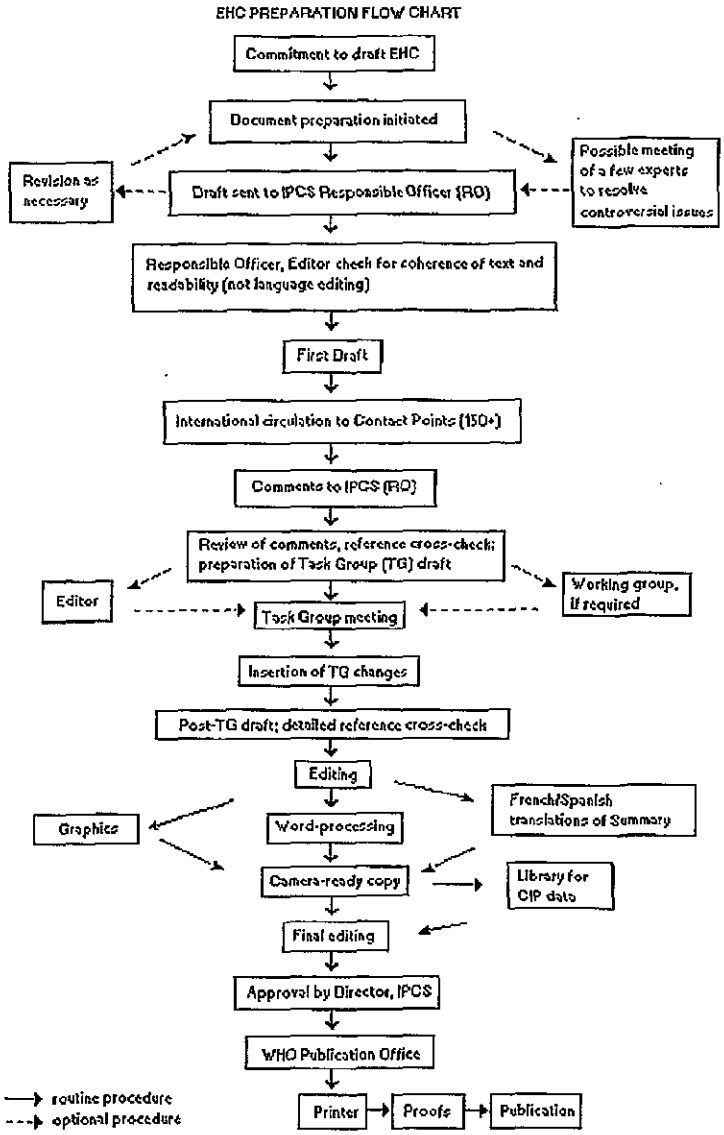
All individuals who as authors, consultants or advisers participate in the preparation of the EHC monograph must, in addition to serving in their personal capacity as scientists, inform the RO if at any time a conflict of interest, whether actual or potential, could be perceived in their work. They are required to sign a conflict of interest statement. Such a procedure ensures the transparency and probity of the process.

When the Task Group has completed its review and the RO is satisfied as to the scientific correctness and completeness of the

document, it then goes for language editing, reference checking, and preparation of camera-ready copy. After approval by the Director, IPCS, the monograph is submitted to the WHO Office of Publications for printing. At this time a copy of the final draft is sent to the Chairperson and Rapporteur of the Task Group to check for any errors.

It is accepted that the following criteria should initiate the updating of an EHC monograph: new data are available that would substantially change the evaluation; there is public concern for health or environmental effects of the agent because of greater exposure; an appreciable time period has elapsed since the last evaluation.

All Participating Institutions are informed, through the EHC progress report, of the authors and institutions proposed for the drafting of the documents. A comprehensive file of all comments received on drafts of each EHC monograph is maintained and is available on request. The Chairpersons of Task Groups are briefed before each meeting on their role and responsibility in ensuring that these rules are followed.



WHO TASK GROUP ON ENVIRONMENTAL HEALTH CRITERIA FOR FLAME RETARDANTS: TRIS(2-BUTOXYETHYL) PHOSPHATE, TRIS(2-ETHYLHEXYL) PHOSPHATE AND TETRAKIS(HYDROXYMETHYL) PHOSPHONIUM SALTS

Members

Dr R. Benson, US Environmental Protection Agency, Denver, Colorado, USA

Dr P. Brantom, British Industry Biological Research Association (BIBRA) International, Carshalton, Surrey, United Kingdom

Dr S. Dobson, Institute of Terrestrial Ecology, Monks Wood, Huntingdon, Cambridgeshire, United Kingdom *(Chairman)*

Professor J. Liesivuori, Department of Pharmacology and Toxicology, University of Kuopio, Kuopio, Finland

Mr D. Renshaw, Department of Health, Elephant and Castle, London, United Kingdom

Dr E. Söderlund, National Institute of Public Health, Department of Environmental Medicine, Oslo, Norway *(Rapporteur)*

Observers

Dr L. Kotkoskic, FMC Corporation, Princetown, New Jersey, USA

Dr P. Martin, Albright and Wilson UK Limited, European Business Services - Product Stewardship, Oldbury, West Midlands, United Kingdom

Secretariat

Dr M. Baril, International Programme on Chemical Safety, Montreal, Quebec, Canada

ENVIRONMENTAL HEALTH CRITERIA FOR FLAME RETARDANTS: TRIS(2-BUTOXYETHYL) PHOSPHATE, TRIS(2-ETHYLHEXYL) PHOSPHATE AND TETRAKIS(HYDROXYMETHYL) PHOSPHONIUM SALTS

A WHO Task Group on Environmental Health Criteria for Flame retardants: tris(2-butoxyethyl) phosphate, tris(2-ethylhexyl) phosphate and tetrakis(hydroxymethyl) phosphonium salts met at the British Industrial Biological Research Association, Carshalton, United Kingdom from 18 to 22 January 1999. Dr P. Brantom opened the meeting and welcome the participants on behalf of the host institute. Dr M. Baril, IPCS, welcomed the participants on behalf of IPCS and the three cooperating organizations (UNEP/ILO/WHO). The Task Group reviewed and revised the draft criteria monograph and made an evaluation of the risk to human health and the environment from exposure to these flame retardants.

Financial support for this Task Group was provided by the United Kingdom Department of Health as part of its contribution to the IPCS.

The first draft of this monograph was prepared by Dr G. J. van Esch, Bilthoven, the Netherlands. The second draft prepared by Dr M. Baril incorporated the comments received following circulation of the first draft to the IPCS contact points for Environmental Health Criteria.

Dr P.G. Jenkins (IPCS Central Unit, Geneva) and Dr M. Baril (IPCS technical advisor, Montreal) were responsible for the overall technical editing and scientific content, respectively.

The efforts of all who helped in the preparation and finalization of the monograph are gratefully acknowledged.

* * *

ABBREVIATIONS

AChE	acetylcholinesterase
ALAT	alanine aminotransferase
ASAT	aspartate aminotransferase
BCME	bis(chloromethyl) ether
BEHP	bis(2-ethylhexyl) phosphate
BMPA	bishydroxymethyl phosphonic acid
BuCHE	butyrylcholinesterase
CHO	Chinese hamster ovary
DMSO	dimethyl sulfoxide
EC_{50}	median effective concentration
FDA	Food and Drug Administration (USA)
GC	gas chromatography
HPLC	high performance liquid chromatography
IC_{50}	median inhibitory concentration
LC_{50}	median lethal concentration
LD_{50}	median lethal dose
LOAEL	lowest-observed-adverse-effect level
LOEL	lowest-observed-effect level
MS	mass spectrometry
nd	not detected
NOAEL	no-observed-adverse-effect level
NOEC	no-observed-effect concentration
NOEL	no-observed-effect level
NPD	nitrogen-phosphorus sensitive detector
NTE	neuropathy target esterase
NTP	National Toxicology Program (USA)
OECD	Organisation for Economic Co-operation and Development
PVC	polyvinyl chloride
SCE	sister-chromatid exchange
TBEP	tris(2-butoxyethyl) phosphate
TEHP	tris(2-ethylhexyl) phosphate
THP	tetrakis(hydroxymethyl) phosphonium
THPC	tetrakis(hydroxymethyl) phosphonium chloride
THPO	trihydroxymethyl phosphine oxide
THPS	tetrakis(hydroxymethyl) phosphonium sulfate
TOCP	tri- *ortho*-cresyl phosphate

PART A

Tris(2-butoxyethyl) phosphate

(TBEP)

A. SUMMARY, EVALUATION AND RECOMMENDATIONS

A1. Tris(2-butoxyethyl) phosphate (TBEP)

A1.1 Summary

Tris(2-butoxyethyl) phosphate (TBEP) is used in floor polishes and as a plasticizer in rubber and plastics. The worldwide production volume is not available but is estimated to be in the range of 5000-6000 tonnes.

TBEP occurs in the environment only as a result of human

activity. Its distribution in the environment has been investigated in certain industrialized countries. Concentrations in surface water were found to be below 300 ng/litre, whereas concentrations in sediment were between 100 and 1000 µg/kg. None of 167 analyses detected TBEP in fish. It has been detected in outdoor air in a single study (<200 ng/m^3). Measurement of TBEP in indoor air in offices showed concentrations of 25 ng/m^3 or less. TBEP is associated with particulates and the source is considered to be the application of floor polish. It has been detected at µg/kg levels in human adipose tissue. The reported daily dietary intake from market basket studies, for a range of age groups, was <0.02 µg/kg body weight per day. Drinking-water concentrations of up to 270 µg/litre have been reported, this is considered to arise from migration from rubber gaskets in the plumbing.

TBEP is considered to be readily biodegradable. Sewage treatment plant measurements and semi-continuous sludge laboratory tests have indicated substantial elimination of TBEP (>80%). In river and coastal water TBEP was completely degraded. The half-life in estuarine water was reported to be about 50 days and there was little degradation in unadapted seawater.

The acute systemic mammalian toxicity and irritation potential are low.

Several subchronic studies in laboratory animals have shown that the liver is the target organ for TBEP toxicity. One study in male Sprague-Dawley rats suggested that TBEP might cause focal myocarditis. Neurotoxic effects in rats after single doses of TBEP are inconsistent. In rats repeatedly given high doses by gavage, TBEP decreased nerve conduction velocity and increased the refractory period. It did not cause delayed neurotoxicity in hens but did inhibit brain and plasma cholinesterases.

Based on an 18-week repeated dose study in rats, the no-observed-effect level (NOEL) for liver effects was reported to be 15 mg/kg body weight per day, while the lowest-observed-effect level (LOEL) was 150 mg/kg body weight per day.

The long-term toxicity and carcinogenicity of TBEP have not been studied.

Bacterial and mammalian cell tests for gene mutation gave negative results, but no tests for chromosomal damage have been reported.

Teratogenicity was not observed in one study in rats. Other aspects of reproductive toxicity have not been reported.

A Repeat Human Insult Patch Test indicated no skin sensitization and minimal skin irritation.

The toxicity of TBEP to aquatic organisms is moderate. The 48-h LC_{50} in *Daphnia magna* is 75 mg/litre and the 96-h LC_{50} values in fish range between 16 and 24 mg/litre.

A1.2 Evaluation

Occupational exposure to TBEP is likely to be by the dermal route during manufacture (accidental exposure) and from the use of floor polishes. The compound is absorbed dermally in experimental animals but no information is available on its kinetics and metabolism. Dermal exposure cannot, therefore, be quantified but is expected to be low. Inhalation exposure in the office environment has been measured to be

25 ng/m³ or less.

Exposure of the general population is principally via food (from use of TBEP as a plasticizer in packaging plastics) and drinking-water (contaminated by leaching from synthetic rubbers used in plumbing washers). Exposure from both sources is very low (estimated to be <0.2 µg/kg body weight per day from the diet and concentrations in drinking-water of <270 µg/litre).

Given the reported NOEL from animal studies of 15 mg/kg body weight per day from a repeated dose oral study, the risk to the general population is very low. The risk to the occupationally exposed is also considered to be very low, though this cannot be quantified.

In the environment, TBEP is expected (from its low volatility, high adsorption coefficient and moderate water solubility) to partition to sediment. The few measured data confirm this. Degradation in environmental media is expected to be rapid. No information is available on breakdown products; phosphate released during breakdown is not expected to contribute significantly to environmental nutrient levels. Fig. 1 plots measured environmental concentrations in surface water against reported acute toxicity values. The margin of safety between highest reported concentrations and lowest reported toxicity values is several orders of magnitude, indicating low risk to organisms in the aquatic environment. No assessment of risk can be made for the terrestrial compartment.

A1.3 Recommendations

For a full scientific evaluation of the compound, identification and assessment of metabolites in mammals would be required, given the toxicological profile of one of the suggested metabolites, 2-butoxyethanol.

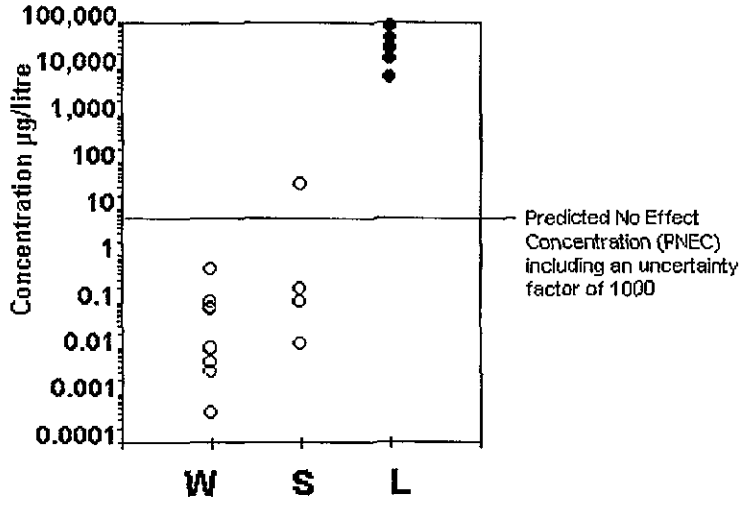


Fig. 1. Plot of measured concentrations in surface waters (W) and sewage effluents (S), and reported acute toxicity values (L) for TBEP (o= measured concentrations in the environment; ● = calculated LC_{50})

A2. IDENTITY, PHYSICAL AND CHEMICAL PROPERTIES, AND ANALYTICAL METHODS

A2.1 Identity