Special Report No 4

1,3-Butadiene
Criteria Document

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ECETOC

SPECIAL REPORT

No. 4

1,3-BUTADIENE CRITERIA DOCUMENT

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European Centre for Ecotoxicology
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PREFACE

This report has been prepared by ECETOC for use by the Commission of the EC DG V and its Scientific Expert Group. It contains an original review and assessment of toxicological data and quantitative risk assessments (chapters 7 to 10) to provide a scientific basis for an occupational exposure limit for 1,3-butadiene (chapter 12). Information on occurrence, production and use, exposure and uptake, and measurement techniques (chapters 3-6) has been drawn largely from existing reviews.

SPECIAL ABBREVIATIONS

1,3-BD	1,3-butadiene
CFU-S	colony-forming assay of stem cells
CFU-GM	CFU of granulocyte/macrophage
CAG	Carcinogen Risk Assessment Group (US EPA)
DEB	1,2:3,4-diepoxybutane
EB	1,2-epoxybutene-3
eMuLV	ecotropic MuLV retrovirus
GSH	glutathione
HLC	haematopoietic and lymphatic cancer
HPLC	high-pressure/performance liquid chromotography
LOEL	lowest-observed effect level
MS	mass spectrometry
MuLV	murine leukemia virus
NOEL	No-observed effect level
NTP I	first mouse study by US National Toxicology Programme (NTP, 1984; Huff *et al*, 1985)
NTP II	second mouse study by NTP (Melnick *et al*, 1990a,b; Melnick and Huff, 1992a), see references not cited: NTP, 1992
PB-PK	physiologically-based pharmacokinetic (model)
SBR	styrene-butadiene rubber
SMR	standard mortality ratio
SCE	sister-chromatid exchange
SLRL	sex-linked lethal
SMART	somatic mutation and recombination test
STEL	short-term exposure limit (15 min, unless specified)
TWA	time-weighted average (concentration) for an 8 h working period
UDS	unscheduled DNA synthesis

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CONTENTS

SUMMARY AND CONCLUSIONS

1,3-Butadiene (1,3-BD) is a colourless, non-corrosive gas with a mildly aromatic or gasoline-like odour. 1,3-BD polymerises readily, especially in the presence of oxygen. The technical product is shipped as a liquified gas under pressure with an inhibitor to prevent polymerisation and/or peroxide formation, such as *p-tert*-butyl catechol.

1,3-BD is not known to occur as a natural product. Industrial emissions arise during (i) production of crude 1,3-BD and petroleum refining, (ii) 1,3-BD monomer production, (iii) transfer of 1,3-BD, (iv) production of 1,3-BD containing polymers, derivatives, rubber and plastic products manufacturing. 1,3-BD has also been identified in automobile exhaust, cigarette smoke, and gasoline formulations, and small amounts are released by the burning of plastics or rubber.

Exposure Levels and Daily Intake

There is limited information on occupational levels exposure in Europe (see below). The Conseil Européen de l'Industrie Chimique (CEFIC), the International Institute of Synthetic Rubber Producers (IISRP) and the Association of Plastics Manufacturers in Europe (APME) have started to collect European exposure data.

In-depth industrial hygiene surveys were conducted by the US National Institute of Occupational Safety and Health (NIOSH) at four monomer and five polymer manufacturing plants. Occupational exposures to 1,3-BD in most process areas were less than 10 ppm; however, maximum 8-h time-weighted average exposures (8-h TWA) were frequently between 10 and 125 ppm (in one case as high as 374 ppm) in operations involving decontamination and maintenance of process equipment, sampling and analysing of quality control samples, and loading or unloading tank trucks or rail cars.

Based on data used to underpin the German TRK value, personal exposure levels (8-h TWA) are approximately 5 ppm, with maxima of 30 ppm during the manufacturing and purification of 1,3-BD in petroleum refineries and extraction facilities. Data from the USA show that many job categories have exposures below or around 5 ppm, the great majority of levels lying below 10 ppm, with the exception of maintenance and distribution jobs. Exposure levels (8-h TWA) associated with manufacturing and use of gasoline are generally very low.

High exposures (5 to 50 ppm, 8-h TWA, max. 500 ppm) occur during the connection of pipes for transfer of 1,3-BD (reported in Germany).

Workplace 8-h TWA concentrations during the manufacturing of 1,3-BD based polymers in Germany were between 10 and 20 ppm (mixture of personal and background measurements), with a maximum (peak) concentration of 50 ppm. Data from 5 polymer plants in the USA showed personal exposure levels generally below 0.5 ppm, with two exceptions at approximately 5 ppm. In two other surveys

of the North American synthetic rubber producers, the majority of exposures was below 10 ppm. The latter picture is confirmed by data collected during health surveys or epidemiological studies. These exposures should not be regarded as representative of conditions in the 1940's, when exposures were higher.

No 1,3-BD could be detected during the manufacturing of tyres from synthetic rubber. The evaporation of 1,3-BD from other plastic products should not constitute a significant source for exposure at end-use.

1,3-BD has been detected in urban air in the USA at ppt to ppb levels. 1,3-BD may also be present in indoor air, e.g. due to cigarette smoking and in drinking water. No residual 1,3-BD could be detected in foodstuffs packaged in materials made from 1,3-BD.

The non-occupational daily intake has been calculated to be 2.62 µg/person, assuming a mean urban air concentration of 0.29 ppb/day (USA data, section 5.3.1) and human air intake of 20 m^3/day.

Measurement

Almost all methods for the sampling of 1,3-BD in air involve the collection of a large volume of contaminated air and concentration of the volatile components, including 1,3-BD (e.g.by adsorption onto charcoal and desorption by methylene chloride). This solution is then separated, and the compounds identified and analysed by gas-chromatography (GC) equipped with a flame ionisation device (FID) or electron capture device (ECD). These methods allow for the detection of very low concentrations, e.g. in the background workplace or ambient air (down to ppt levels) (HSE, CONCAWE and NIOSH methods).

For personal monitoring at the workplace, gas detector tubes are used.

Toxicity

There is an extensive data base on the toxic effects of 1,3-BD. Toxicological studies have revealed a remarkable difference in sensitivity to 1,3-BD between the mouse and all other species investigated.

The metabolic elimination of 1,3-BD is linearly related to the ambient exposure concentration up to about 1000 ppm in rats and mice, with mice showing higher elimination rates. Above 1000 ppm, metabolic pathways are approaching saturation in these species. In monkeys the metabolic elimination of 1,3-BD appears to be saturated at about 300 ppm. The biotransformation appears to be qualitatively similar across species, including humans. However, differences in uptake and kinetics of 1,3-BD result in quantitative difference in body burden of 1,3-BD and its individual metabolites across species. For the metabolite 1,2-epoxybutene (EB) the body burden in the mouse appears to be threefold higher than for the rat. *In vivo* data on primates and *in vitro* data on human samples suggest that humans are

closer to the rat than the mouse with regard to metabolism and resulting body burden of EB.

Upon inhalation, 1,3-BD has a low acute and subchronic toxicity. The target organs in the mouse are the central nervous system (CNS) and the bone marrow, whereas in the rat non-specific effects were reported.

1,3-BD itself is not genotoxic. The genotoxic action of 1,3-BD in various test systems depends on its biotransformation to reactive metabolites. Some of these metabolites apparently have the ability to directly interact with DNA and cause gene-mutations and chromosomal aberrations. When comparing the results of *in vivo* tests performed with 1,3-BD, its genotoxic activity has been demonstrated clearly in the mouse and equivocally in the hamster, but not in other species.

The carcinogenic effects after (life-time) inhalation of 1,3-BD were studied in Sprague-Dawley rats and in B6C3F1 mice. The species differences between mice and rats were also observed in these studies. 1,3-BD is a potent carcinogen in mice with tumours found in lungs of females at 6.25 ppm, the lowest concentration tested. At higher concentrations tumours were found at multiple sites. In contrast, 1,3-BD is less potent in rats, where statistically significant increases in tumour incidences were observed at 1000 ppm and 8000 ppm. The tumour pattern in both sexes of the rat suggest that a hormone-related mechanism is involved. The only tumours seen at 1000 ppm with statistically significant increases were mammary gland tumours in the female. The majority of these tumours were benign. There was neither a significant increase of benign nor of malignant tumours when considered separately. Based on this information 1000 ppm is a NOEL for the rat.

Special studies designed to assess fertility did not show adverse effects in guinea pigs, rabbits and rats. Developmental toxicity studies conducted with 1,3-BD show that there was no toxicity to the developing foetus at exposure concentrations below those which caused maternal toxicity. Overall these studies show again the unique susceptibility of the mouse to 1,3-BD.

With regard to the epidemiological studies, some authors recognised a qualitative association between 1,3-BD exposure and haemotopoietic and lymphatic cancer, while others see no causal relationship. The available studies, however, are inappropriate for quantitative risk assessment since, in the absence of measured concentrations, the exposure data were only qualitative.

Quantitative Risk Assessment (Models)

Numerous quantitative risk assessments with regard to the carcinogenicity of 1,3-BD have been carried out. The range of risk values determined using the mouse bioassay are incompatible with findings of the epidemiological studies. Values for extrapolation on the rat bioassay also show some variation for the best estimated lifetime risk. The predictive value of mathematical models used for extrapolation of animal bioassay data to low human exposure is questionable because the models (i) are not validated, (ii) are derived from mathematical assumptions rather than

knowledge of biochemical mechanisms, (iii) demonstrate a wide variety of risk estimates depending on the models used, and (iv) give the impression to be precise which cannot be justified from the approximations and assumptions upon which they were based. Until these concerns are adequately addressed, this type of quantitative risk assessment in unsuitable as a basis for setting an exposure limit.

Final Evaluation and Recommendation

With regard to the effects of 1,3-BD on experimental animals, it is obvious that the mouse is more sensitive than all other species investigated. This holds true for subchronic toxicity, reproductive toxicity, genotoxicity and carcinogenicity. Based on the results of *in vivo* genotoxicity tests performed with 1,3-BD, it has to be assumed that the potency of 1,3-BD to induce genotoxic effects in mice is higher than in other species. Mechanistic data indicate that differences in metabolism, both in the formation and removal of the epoxides, are in part responsible for this difference in susceptibility. Based on the toxicokinetic data available for a comparison of species including humans, the rat appears to be an acceptable conservative model on which to base an exposure limit value for humans.

The carcinogenic potential of 1,3-BD is clearly the dominant concern of health effects related to 1,3-BD exposure. There is some doubt whether genotoxic action is the critical mechanism for induction of tumours in the rat. This is substantiated by the tumour pattern observed in the rat which is more indicative of an indirect mechanism mediated through the endocrine system. However, resolution of this issue is not possible on the basis of the available information.

The uncertainties discussed above make it difficult to derive a scientifically sound occupational limit. The lowest occupational exposure limit used in EC member states today is 5 ppm (German TRK value for certain applications; based on technical feasibility). This concentration is 200-fold lower than the identified NOEL in the rat. In addition, with all the reservations expressed above considered, the quantitative risk assessments based on the rat bioassay suggest that the risk of additional cancer deaths at 5 ppm is low. Most important perhaps, epidemiological data generally do not demonstrate any excess mortality from all causes, all cancers or any other broad category of disease for past exposure concentrations which were most likely higher than the current exposure concentrations. The controversy with regard to the possible association between 1,3-BD exposure and haematopoietic and lymphatic cancer, which has been proposed by some authors and rejected by others, still has to be resolved.

In view of all the available evidence, it is concluded that an occupational exposure limit (OEL) of 5 ppm should protect workers against non-neoplastic and neoplastic effects.

The ongoing research programme will add significantly to the understanding of the mechanism and toxicokinetics of 1,3-BD-induced carcinogenesis, and provide information on exposure-based epidemiology. Thus, the OEL should be re-

evaluated after this new information will have been incorporated into the database. This work should be completed by 1995.

Since skin absorption of 1,3-BD is not a concern, no skin notation is suggested.

There is no evidence to suggest that it is critical to determine a short-term exposure limit (STEL). However, because of the uncertainty about the biological relevance of high short-term exposures to 1,3-BD, a STEL of 100 ppm (15 min TWA) is recommended as a complimentary control to the OEL of 5 ppm.

At present, no method for biological monitoring can be recommended.

A number of suitable methods are available for carrying out short-term, long-term and continuous sampling measurements of 1,3-BD at the recommended OEL of 5 ppm (section 6.1).

1. SUBSTANCE IDENTIFICATION

1.1 Identity

Common name:	1,3-butadiene
CAS name:	1,3-butadiene
CAS registry N°:	106-99-0
EEC N°:	601-013-00-X, nota D
EEC classification:	F+ ; R 13 / Carc. Cat. 2; R 45
EEC labelling:	R: 45-13 S: 53-9-16-33
RTECS N°:	EI 9275000
IUPAC name:	1,3-butadiene
EINECS name:	buta-1,3-diene
EINECS N°:	203-450-8

Synonyms and trade names:

DA:	1,3-butadien
DE:	1,3-Butadien
EL:	1,3-βουταδιένιο
EN:	biethylene bivinyl butadiene butadiene, inhibited butadiene-1,3 α,γ-butadiene *trans*-butadiene diethylene divinyl erythrene NCI-C50602 pyrrolylene vinylethylene
ES:	1,3-butadieno
FR:	1,3-butadiène
IT:	1,3-butadiene

NL: PT:	1,3-butadieen 1,3-butadieno
Chemical group:	unsaturated hydrocarbons
Formula:	C_4H_6
Structure:	$CH_2{=}CH{-}CH{=}CH_2$
Molecular mass:	54.09 (Weast *et al*, 1988)
Purity of technical product:	99.8% (min. 99.5%) (ICI, 1992)
Impurities of technical product:	1,2-butadiene, max. 20 ppm peroxides (measured as H_2O_2), max. 5 ppm acetylene, max. 25 ppm sulphur, max. 2 ppm C5's, max. 0.1% w/w butadiene dimer, max. 0.05% w/w non-volatile residues (such as trimer), max. 500 ppm Carbonyl (as acetaldehyde), max. 25 ppm propadiene, max. 10 ppm water, some (ICI, 1992)
Inhibitor:	75-150 ppm of *p-tert*-butyl catechol (ICI, 1992)