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HEALTH & CONSUMER PROTECTION DIRECTORATE-GENERAL  
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**C7 - Risk assessment**

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**SCIENTIFIC COMMITTEE ON TOXICITY, ECOTOXICITY AND THE  
ENVIRONMENT (CSTEE)**

**Opinion on the results of the Risk Assessment of:**

**BUT-2-YNE-1,4-DIOL  
HUMAN HEALTH PART**

**CAS N°: 110-65-6**

**EINECS N°: 203-788-6**

**Carried out in the framework of Council Regulation (EEC) 793/93 on  
the evaluation and control of the risks of existing substances<sup>1</sup>**

**Adopted by the CSTEE during the 39<sup>th</sup> plenary meeting  
of 10 September 2003**

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<sup>1</sup> Regulation 793/93 provides a systematic framework for the evaluation of the risks to human health and the environment of those substances if they are produced or imported into the Community in volumes above 10 tonnes per year. The methods for carrying out an in-depth Risk Assessment at Community level are laid down in Commission Regulation (EC)1488/94, which is supported by a technical guidance document.

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## **Terms of Reference**

In the context of Regulation 793/93 (Existing Substances Regulation), and on the basis of the examination of the Risk Assessment Report the CSTEE is invited to examine the following issues:

1. Does the CSTEE agree with the conclusions of the Risk Assessment Report
2. If the CSTEE disagrees with such conclusions, the CSTEE is invited to elaborate on the reasons for this divergence of opinion.

## **INTRODUCTION**

About 200,000 tonnes of But-2-yne-1,4-diol ("Butynediol") are annually produced in Europe. Butynediol is used as a chemical intermediate, mainly (98%) to make butanediol and butenediol. About 2% are used in the chemical synthesis of polyols, flame retardants, auxiliaries for the paint and textile industry, and in products for metal surface treatment, and cleaning products.

## **GENERAL COMMENTS**

The human health part of the document is comprehensive and written in accordance with the principles of the Technical Guidance Documents. Some inconsistencies in the exposure and effects assessment parts have to be resolved, however, and more detail is requested with regard to the toxicokinetics section. The CSTEE agrees with most of the proposed conclusions, except for those regarding systemic toxicity (some scenarios) and genotoxicity and carcinogenicity (all scenarios). The rationale is given below.

## **SPECIFIC COMMENTS**

### **Exposure assessment**

Butynediol is produced at two sites in Europe, with a total production volume of about 200,000 tonnes. There is no import from outside EU, and less than 300 tonnes were exported (1993). Butynediol is produced in closed systems at 80-100 °C from aqueous formaldehyde and acetylene under conditions of high pressure. 98% of the produced are processed on-site to make butanediol and butenediol. The remaining 2% (4,000 t) are used in the form of flakes or as 32-34% aqueous solutions to make polyols, flame retardants, auxiliaries for the paint and textile industry, brightening agents, and products for metal surface treatment, and cleaning products.

Thirteen occupational exposure scenarios are described in the RAR: two are for the production and further processing (one refers to solutions, the other to the solid in form of flakes), two are for further processing to formulations, and nine refer to the use of formulations.

Inhalation exposure is highest during production (drumming of flakes), and during repair and maintenance work with measured data  $\leq 1 \text{ mg/m}^3$  (8-hr TWA). Highest dermal exposures were identified for the preparation of formulations (34% aqueous solutions), with an estimated 143 mg/person/day as a worst case based on EASE calculations for the unprotected worker.

Consumer products that may contain butynediol include cleaning products (for cars, buildings, sanitary installations), disinfectants, and descaling agents, with reported maximum concentrations of up to 5% (in descaling agents). It is noted that some discrepancies with regard to the use concentrations in consumer products are found between chapters 2 and 4.1.1.1. Furthermore, the wording in the RAR is not clear as to whether some of these products are sold in spray form.

Combined total inhalation and dermal exposure of consumers from the use of liquid descaling and cleansing products was calculated to be about  $0.03 \text{ }\mu\text{g/kg bw/day}$  with the CONSEXPO model. From the information presented it is not clear which use concentrations have been used to derive these values. Furthermore, the RAR does not include a discussion on a potential exposure through spray products.

For the vicinity of a point source, a local dose of  $0.004 \text{ mg/kg bw/day}$  was calculated for the exposure via the environment, compared with a regional background dose of  $0.008 \text{ }\mu\text{g/kg bw/day}$ .

## **Effects assessment**

### ***Toxicokinetics and biochemical effects.***

Butynediol can be absorbed via the oral, dermal and respiratory routes, but there is no quantitative data on the extent of absorption available. Information on absorption is presented in the risk characterization section, but should be added (together with references) also to section 4.1.2.1. In contrast to the statement in the exposure section, the RAR refers to a "relevant inhalatory exposure due to the vapour pressure of butynediol", and a slightly different value for the vapour pressure is presented in this section as compared to the previous text ( $0.17 \text{ Pa}$  on page 10,  $2.0 \text{ Pa}$  on page 40, approx.  $0.17$  on page 67). The inconsistencies in the text need to be resolved, and all values presented in the toxicokinetics part should be referenced.

Further to the information presented in this section, there is additional data on the metabolism of butynediol, that should be discussed in the RAR (Taberner and Pearce, 1974; Bradbury and Christensen, 1991).

### ***Acute toxicity***

In animal studies, butynediol was toxic by inhalation and if swallowed and harmful in contact with skin. There is no information on accidental human exposure.

### ***Irritation/corrosion***

Butynediol (in concentrations  $\geq 50\%$ ) is corrosive to the skin and can induce serious damage to eyes. Respiratory irritation was observed in subacute animal studies.

## ***Sensitisation***

Butynediol was a weak skin sensitizer in guinea pigs and humans. No information is available as to its potential for respiratory sensitization.

## ***Repeated-dose toxicity***

Liver, kidneys and - after oral exposure - the hematopoietic system have been identified as the target organs after repeated exposures to butynediol. From a 28-day oral study on rats, a NOEL of 1 mg/kg bw/day was derived (LOAEL: 10 mg/kg bw/day). No systemic toxic effects were seen in a 30 day inhalation study on rats at 25 mg/m<sup>3</sup> (= 7.2 mg/kg bw), at 300 mg/m<sup>3</sup> liver and kidney toxicity was evident. Local effects included metaplasia and inflammation of the larynx at concentrations  $\geq$  5mg/m<sup>3</sup> (NOAEC<sub>loc</sub>: 0.5 mg/m<sup>3</sup>).

Current standard neurofunctional tests and histopathology of neural tissues gave no indication of a neurotoxic effect, and hence did not support earlier and not well-documented neurotoxicity findings (histomorphologic brain lesions, delayed reflexes).

The RAR states (p.83), that “there is concern that butynediol induces significant health damage after prolonged inhalation exposure..... The need for classification should be reconsidered when new data are available filling the data gaps identified”. This statement warrants a conclusion (i) and should therefore be elaborated on. The RAR should discuss more extensively the referred data gaps.

## ***Genotoxicity***

In vitro, butynediol was not mutagenic in a standard Ames test with four strains of Salmonella typhimurium in the presence and in the absence of a metabolic activation system (rat liver S-9 mix). In Chinese hamster V79 cells, no clastogenic activity was found without S-9 mix, whilst contradictory results were obtained in experiments in the presence of metabolic activation (two experiments with positive result, one with a negative result).

In vivo, no increase in the frequency of micronucleated cells was induced in bone marrow of NMRI mice in a study performed in accordance with the current guideline, using a single intraperitoneal injection of the test chemical (17.5, 35, 70 mg/kg bw). The RAR states that “toxic reactions were expressed at 70 mg/kg bw, but does not provide further details or proof that the target tissue has been reached.

Based on these data, the member states' rapporteur concluded that “there is no relevant concern with respect to germ cell mutagenicity of butynediol”.

The CSTEE finds that the lack of concern with regard to the genotoxicity endpoint is not sufficiently justified in the RAR. Butynediol seems to be activated to a toxic metabolite in liver by liver aldehyde dehydrogenase (ADH) (Taberner and Pearce, 1974; reference not in the RAR). Badbury and Christensen (1991) proposed that enzymatically formed 4-hydroxy-2-butyral, a potent electrophile was responsible for the inactivation of alcohol oxidase by butynediol. It is therefore questionable whether a single injection and the use of the intraperitoneal route in the in vivo test were adequate to rebut concerns about the genotoxicity of this chemical. Furthermore, the information as provided is insufficient to prove that the target tissue has been reached.

## ***Carcinogenicity***

Butynediol has not been tested in carcinogenicity studies and there is no epidemiology data available.

Though limited by short duration, the early dermal tumour initiation-promotion study by Roe (1957) has not been included in the RAR. No tumour initiating effect was found in mice after application of butynediol once a week for 10 weeks. From the second study week onwards croton oil was applied for a total of 18 weeks.

## ***Toxicity for reproduction***

Effects of butynediol on reproduction and development were investigated on rats in a 1-generation study according to OECD TG 415, and in a developmental toxicity study according to OECD TG 414. No effects on fertility were found (NOAEL 40 mg/kg bw/d; highest dose tested), nor were there any effects on the development (NOAEL 80 mg/kg bw/day; highest dose tested).

## **Risk characterisation**

Butynediol exposure levels in the various exposure scenarios were compared with “minimal MOS values”. The RAR explains how the minimal MOS-values were derived, based on adjustment factors and an uncertainty factor. For repeat dose systemic effects an adjustment factor of only 2 was chosen for chronic exposure scenarios, as there was no indication for a substantially different threshold between subacute and subchronic exposures (based on results from oral studies), and minimal MOS values of 12 and 40 have been used for inhalation and dermal exposures, respectively. The minimal MOS of 12 was derived using an adjustment factor of 2 for the breathing volume, a factor of 2 for the duration, and an overall uncertainty factor of 3 (because there was no need for route-to-route extrapolation). The minimal MOS of 40 for dermal exposure was derived using a factor of 4 for the metabolic rate scaling, a duration factor of 2, and an uncertainty factor of 5. For local effects the duration adjustment factor was chosen as 1, based on no evidence of an increase in the severity of lesions when rats were exposed from one to four weeks in inhalation studies (The CSTEE notes that there was, however, an increase in the incidence of the lesions).

The CSTEE points to the fact that the use of some of the adjustment and uncertainty factors lacks a proper justification and seems arbitrary, and may therefore not be defensible. In particular, the rationale for choosing uncertainty factors of 5 and 3 is not transparent, and the use of duration adjustment factors of only 2 and 1 (instead of 6) is questioned.

## **Workers**

The risk characterisation has been performed for the main routes of exposure, i.e. the inhalation and dermal routes.

## ***Acute toxicity***

Comparisons of estimated worker exposures with animal inhalation LC50 values result in a MOS value of about 100. The MOS for the dermal route was calculated as 323 based on estimated worst case worker exposures and a dermal LD50 value in rabbits of  $\geq 659$  mg/kg bw.

The CSTEE agrees with conclusion (ii).

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### ***Irritation/corrosion***

Personal protective equipment (gloves, eye protection) is obligatory when handling butynediol. The CSTE agrees with conclusion (ii).

A “borderline concern” was identified with regard to respiratory tract irritation for scenarios in which butynediol is handled as a solid substance. The CSTE is in agreement with conclusion (iii) for these scenarios.

### ***Sensitisation***

Butynediol is a weak skin sensitizer. Conclusion (iii) has been derived for all scenarios with butynediol concentrations of greater than 1%. The CSTE agrees with conclusion (iii) for these scenarios. The CSTE agrees that there is no evident concern for respiratory sensitisation.

### ***Repeated-dose toxicity***

For local effects by repeated inhalation of butynediol, MOS values of 0.5 and 0.8 were calculated for exposures in the production and processing of flakes (scenario 2) and in the preparation of formulations (without LEV) (scenario 3b), and conclusion (iii) was derived for these scenarios. The CSTE is in agreement with the proposed conclusions.

The lowest calculated MOS values for systemic effects after inhalation and dermal exposure were 25 and 39 (for scenarios 2 and 1), respectively. It is noted, that with the conventional factor of 100 for the minimal MOS, these values arise concern. As pointed out above, there are uncertainties in the derivation of the minimal MOS values as presented in the RAR. Until these uncertainties have been resolved, the CSTE cannot support conclusion (ii) for these two scenarios, and considers **conclusion (iii)** as more appropriate.

The CSTE is in agreement with conclusion (ii) for the other exposure scenarios.

### ***Genotoxicity***

Based on equivocal results from in vitro chromosome aberration studies, and concerns about the adequacy and relevance of the available negative in vivo micronucleus test, the CSTE recommends **conclusion (i)** for the genotoxicity/carcinogenicity endpoints.

### ***Carcinogenicity***

In the opinion of the CSTE the lack of concern for carcinogenicity needs further justification, as it is presently based solely on the alleged lack of a genotoxic activity. Given the overall toxicity profile with indications of a potentially genotoxic metabolite, and the possibility of sustained cell proliferation due to irritant effects, further mechanistic data would need to be presented for a sound evaluation of this endpoint. **Conclusion (i)**.

### ***Toxicity to Reproduction***

The CSTE agrees with the conclusion of the RAR that there are no specific concerns with regard to this endpoint (conclusion ii).

### **Consumers**

The CSTEE agrees, in principle, with the conclusions for consumer scenarios as presented in the RAR. However, inconsistencies in the reported use concentrations (see above) will have to be resolved and, if then necessary, the values will have to be re-calculated. If relevant, exposure through spray products needs to be addressed.

### **Man exposed indirectly via the environment**

The CSTEE agrees with conclusion (ii).

### **REFERENCES**

Bradbury SP, and Christensen GM (1991). Inhibition of Alcohol Dehydrogenase Activity by Acetylenic and Allylic Alcohols. Concordance with in vivo Electrophile Reactivity in Fish. Environ. Toxicol. Chem. 10, 1155-1160.

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Taberner PV and Pearce (1974). Hypothermic and toxic actions of 2-Butyne-1,4-diol and other related Diols in the Rat. J. Pharm. Pharmacol. 26, 597-604.