EUROPEAN COMMISSION

Health & Consumer Protection
Directorate-General

Scientific Committee on Health and Environmental Risks

SCHER

2-buthoxyethanol (EGBE)
Human Health Part

CAS Number: 111-76-2
EINECS Number: 203-905-0

Scientific Committees
on consumer products
on emerging and newly identified health risks
on health and environmental risks

Opinion adopted by the SCHER during the 22nd plenary of 12 March 2008

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Three independent non-food Scientific Committees provide the Commission with the scientific advice it needs when preparing policy and proposals relating to consumer safety, public health and the environment. The Committees also draw the Commission's attention to the new or emerging problems which may pose an actual or potential threat.

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SCHER

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TABLE OF CONTENTS

1. BACKGROUND

Council Regulation 793/93 provides the framework for the evaluation and control of the risk of existing substances. Member States prepare Risk Assessment Reports on priority substances. The Reports are then examined by the Technical Committee under the Regulation and, when appropriate, the Commission invites the Scientific Committee on Health and Environmental Risks (SCHER) to give its opinion.

2. TERMS OF REFERENCE

The SCHER on the basis of the examination of the Risk Assessment Report is invited to examine the following issues:

1. Does the SCHER find the conclusions of the targeted risk assessment appropriate?
2. If the SCHER finds any conclusion not appropriate, the SCHER is invited to elaborate on the reasons for this divergence of opinion.
3. If the SCHER finds any specific approaches or methods used to assess the risks inappropriate, the SCHER is invited to suggest possible alternative approaches or methods meeting the same objectives.

3. OPINION

3.1 General Comments

The health part of the document is of good quality and both the exposure and effects assessment follow the TGD.

EGBE (as 2-buthoxyethanol is named within the RAR) is a relatively high production volume compound. It is currently produced by many companies in the European Union, where the estimated production volume is about $1.5x10^5$ tons/y. As a solvent, it is used in many industrial activities or consumer applications. The main uses are in paints or surface coatings, followed by cleaners and printing inks. The main use categories were: paints, varnishes and inks, cleaning agents and products for metallurgical and mechanical sectors, e.g. grease cleaners. A number of minor uses have also been reported.

3.2 Specific Comments

3.2.1 Exposure assessment

EGBE is a neutral, colourless liquid with a very weak pleasant odour and a relatively low vapour pressure (0.1 kPa at 20°C).

Humans may be exposed to EGBE at workplace, via consumer products and indirectly via the environment. The highest potential exposure is likely to occur during occupational exposure via inhalation and dermal routes. Since EGBE is readily absorbed through the skin from direct contact with liquid, with aerosol form or with vapours, dermal absorption may contribute significantly to overall exposure. For this reason, environmental monitoring of breathing zone or air concentrations in the work area has been found to be inadequate to assess overall exposures the total exposure to EGBE. Biological monitoring of the common toxic urinary metabolite, 2-butoxyacetic acid (BAA), is considered more reliable for a complete exposure assessment.

The SCHER agrees with the choice of three main categories of scenarios regarded to be relevant for occupational exposure, that is:

(a) EGBE manufacturing and its use as an intermediate.

Air sampling data are available from a number of sources showing very low workplace air levels; measured inhalation exposure data have been compared with those predicted from

the EASE model. Due to automated processes for feeding reactors and for drum and tanker filling, typical inhalation exposure is<0.5 ppm. Higher exposure may occur during non-routine maintenance activities or during rare incidents such as spills or leaks. Based on available measured data the value of 2.4 ppm (12 mg/m^3) has been proposed as a worst-case TWA atmospheric concentration in production activities.

To predict occupational dermal exposure to EGBE, the available measured data have been considered together with modelling. Due to the enclosure of the process and control measures taken to minimize skin contact, dermal exposure at the plant is incidental and generally low. The EASE model estimated a dermal exposure in the range of 0-0.1 mg/cm^2/day (corresponding to 42 mg/day maximum external dermal exposure, assuming exposed skin surface area is 420 cm^2). Dermal exposure estimates provided by EASE do not take into account evaporation of the product, giving an overestimation of dermal exposure. This exposure will be mitigated by the use of suitable gloves.

(b) The formulation of products containing EGBE.

Measured data from a high number of companies are available from which it appears that exposure strongly depends on the process, which may be closed or relatively open. Based on air sampling data, monitoring data, database values and modelling, a worst case inhalation exposure=3.2 ppm (15.7 mg/m^3) has been estimated during formulation of products containing EGBE. Typical exposure levels are probably much lower (<1 ppm).

Concerning dermal exposure, measured data are available on DGBE (performed in the frame of the “Riskofderm” project), which indicate 11,600 mg/day as the exposure levels although a high degree of variability is evidenced. The SCHER considers those data not fully representative for EGBE dermal exposure, since measurements have been done with workers wearing cotton gloves, which are not DPI and may increase skin contact, and because of the different vapour pressure of the two chemicals, giving rise to overestimation. Although limited biomonitoring data on EGBE indicate a dermal exposure of 500 mg/day similar to what can be obtained by using EASE modelling. The RAR proposed to take the available Riskofderm data as a basis and to adapt them to EGBE using biomonitoring data: doing so data on biomonitoring are corrected by a factor of 4, eventually leading to skin penetration of 2,000 mg/day. The SCHER considers the adoption of the correction factor unjustified and not based on solid scientific ground.

(c) The use of products containing EGBE.

Exposure due to the use of different products containing EGBE may be extremely variable, due to differences in frequency and duration of use, concentration of EGBE in the products, method of application/use and precautions taken during use.

The SCHER agrees on the inhalation exposures associated with each sub-scenario depending on the type of products. On the other hand, SCHER expresses some doubts on the use of Riskofderm data and the correction made to adapt the biomonitoring data to them.

Consumer exposure

An extensive data base of measured data is available for the three different scenarios, that is household surface cleaners, indoor air, and painting. The SCHER agrees with the RAR conclusions on reasonable worst cases.

Indirect exposure through the environment

Both local and regional levels in intake media (drinking water, fish, plant roots and leaves, milk, meat, air) and the subsequent estimation of human intakes via different routes have been taken into consideration.

3.2.2 Effect assessment

Orally administered EGBE is quantitatively absorbed from the gastrointestinal tract in man. Absorption of 100% for the oral route is proposed to be taken for the risk characterisation.

From dermal absorption studies, a wide range of absorption values were observed, depending on the species (rats having a 2-3 fold greater dermal penetration than humans), the dilution of EGBE (40 % or 80 % water solutions of EGBE being absorbed at twice the rate compared to undiluted EGBE) and EGBE physical state. In rats dermal absorption of liquid EGBE varies between 20 to 30 % of applied dose; in volunteers a percentage of internal dose due to dermal absorption of vapour EGBE ranging between 11 and 39 % of the dose has been reported. These data have been confirmed by the use of a PBPK model. The highest values (30% for the liquid and 39% for the vapour) have been considered for the risk characterization. The SCHER agrees, although in the awareness that they represent conservative values.

From human volunteer inhalation studies, absorption of 55 % to 60 % has been measured: the highest value is proposed to be taken for the risk characterisation.

For interspecies extrapolation, experimentally validated PBPK models exist for the rat, mouse and human (Corley et al. 1994, 1997; Lee et al. 1998). These enable the internal dose of EGBE and of its major toxicologically relevant metabolite BAA, to be estimated with some precision, following oral and inhalation exposure. The SCHER supports the use of these conclusions in the risk characterization.

EGBE is rapidly metabolised (with a plasmatic half life of about an hour) The main metabolic pathway leads to the formation of BAA catalysed by alcohol dehydrogenase and aldehyde dehydrogenase, followed by formation of glucuronide conjugates of BAA (but also of parental EGBE at high concentrations). Elimination is rapid and mainly via urinary route (80 to 90 % of the metabolites). The plasmatic half-life of metabolites is about 4 hours. A small amount (10 to 20 %) is eliminated as CO_2 in the expired air.

In acute toxicity studies, EGBE causes haemolytic anaemia, independently on the species and the route of administration. A number of in vitro and in vivo mechanistic studies indicated that BAA is responsible for EGBE-induced haematological effects. Regarding EGBE acute oral, dermal and inhalation toxicity, the SCHER agrees with the conclusion that EGBE is to be classified as harmful and labelled with R20/21/22, proposed on the basis of results from studies on experimental animals. Some acute toxicity data are also available for human via ingestion and inhalation. For the oral route case reports indicated that clinical symptoms (i.e. metabolic acidosis, SNC depression, and in some cases signs of haemolysis) were seen between 0.5 and 4.5 g/kg bw. A LOAEL of 400 mg/kg bw can be taken into account for acute toxicity by oral route in humans in the risk characterisation section, based on induction of acidosis.

SCHER agrees that EGBE is a skin and an eye irritant and that appropriate labelling with R38 and R36 is necessary. Animal studies did not show any signs of significant respiratory irritation; however, on the basis of human data a NOEL of 50 ppm for respiratory irritation is taken forward for risk characterisation. SCHER disagrees with this conclusion and considers EGBE not to be a respiratory irritant: indeed, no effects were described in 3 recent studies when human volunteers were also repeatedly treated with EGBE (up to 50 ppm, the highest dose tested). Only one study, dated 1955, reported that 3 individuals treated with 100 and 200 ppm experienced some irritation, but whether such ‘irritation’ was physiological or merely discomfort is not indicated.

Based on the results of animal and human studies, EGBE did not result as a skin sensitizer.

For the assessment of DPA repeated dose toxicity, data are reported after oral, dermal and inhalation route. In rodents haemolysis was consistently observed (whichever the route of administration) and considered as the critical effects for NOAEL derivation. It was sometimes associated with hepatic effects, effects on the forestomach, and effects on the WBC sub-populations (T lymphocyte). Data on humans are also available, indicating that

man is less sensitive than rats and mice to the haemolytic properties of EGBE. This is confirmed by in vitro studies, indicating that in response to BAA, human erythrocytes in culture are less sensitive than the rodent cells by at least an order of magnitude. However, no other specific toxic effects could be identified

For the inhalation route a NOAEC of 25 ppm (121 mg/m^3) and a LOAEC of 31 ppm (150 mg/m^3) were identified in two separate 13-week studies with rats. The same LOAEC was derived also in a chronic inhalation studies with rats (104 weeks); this value has been taken forward to risk characterization.

For the dermal route, a NOAEL of 150 mg/kg bw/d (the highest dose tested) has been determined from a 13-week study in rabbits. For the oral route, a LOAEL of 69 mg/kg/day for rats was found in a 13 -week drinking water study. No long term studies are available on these two routes.

Genotoxicity studies in bacteria and mammalian cells with EGBE and its metabolite BAA were mostly negative. Positive results were reported in some poor quality studies, using extremely high concentrations (20 mM) or incorrect experimental protocols. Negative results from an in vivo micronucleus test indicate that no mutagenic effects are expressed in vivo. On the basis of whole amount of data, SCHER agrees that EGBE should be not considered as genotoxic.

Chronic/carcinogenicity studies are available following inhalation in rats and mice. In rats no NOAEC could be derived for non-neoplastic effects and the LOAEC for inhalation was 31 ppm (151 mg/m^3), based on an increased incidence of Kupffer cell pigmentation and on significant haematological effects. The report concludes that there was no evidence for carcinogenicity in male rats and equivocal evidence for carcinogenicity in female rats, due to the presence at 125 ppm (604 mg/m^3, a 4-fold higher dose than the LOAEC) of small phaeochromocytomas, mostly not distinct from adrenal medullary hyperplasia.

Similarly in the mouse study, no NOAEC could be derived for non-neoplastic effects, the LOAEC being 62.5 ppm (150 mg/m^3), based on marginal, but significant, haematological effects. The NOAEC for tumourgenicity in mice is 125 ppm (302 mg/m^3), based on an increased incidence of haemangiosarcomas (8%) in males and squamous cell papillomas or carcinomas in females at 250 ppm.

Since EGBE is not genotoxic, it can be hypothesised that its carcinogenic action, when delivered as a vapour, has a threshold. The experimental data clearly indicated that the NOAEC values for carcinogenicity are higher than those based on non-neoplastic effects (i.e. haematological effects, mediated by BAA). Furthermore, EGBE induces tumours of the forestomach in female mice and haemangiosarcomas of the liver in male mice and neither of these tumours occur in the other gender in mice or in rats.

Consistently with the available data, the RAR proposed haemosiderin deposition consequent to BAA-induced haemolysis as a mechanism for haemangiosarcomas observed in male mice. Haemosiderin deposition in relevant cell-types, including endothelial cells from which haemangiosarcomas arise, and the generation of cytotoxic reactive oxygen species may either induce indirect oxidative genetic damage or sustained cell proliferation within the endothelial target tissue, neoplasia arising out of this proliferating cell population.

Since man is much less sensitive to the haemolytic effects of EGBE, the low level of haemangiosarcomas induced only in male mice might have a limited relevance for human risk assessment. In addition, reference values protecting from induction of haemolysis and anemia should be considered protective also for the tomorigenic effects.

The proposed mechanism of action for squamous cell papilloma and a single squamous cell carcinoma of the forestomach in female mice is the local generation, as well as accumulation of cytoxic metabolite(s) that induce a sustained, compensatory cell proliferation.

A relevant kinetic difference occurs between rat and mouse stomach, that is the much higher affinity constants of murine alcohol dehydrogenase activity (up to an order of

magnitude) and the higher V_{max} value, when using EGBE as the substrate Therefore, there is greater potential for EGBE to be metabolised to BAA in the forestomach of mice than in the rat one. The mechanism proposed for the induction of forestomach tumours would also point to a lack of human relevance. Indeed, although it is not possible to use as a justification the fact that human do not possess forestomach (due to the presence of comparable squamous epithelial tissues in the oral cavity and the upper two-thirds of the oesophagus), EGBE acts with a non genotoxic mechanism, that is likely linked to the permanence and *in situ* metabolism in the forestomach.

The SCHER agrees that EGBE has not to be considered as a human carcinogen, due to the species and sex specificity of the neoplastic responses and the current evidence supporting the hypothesis that the more likely mechanism of action is based on haematotoxicity.

EGBE showed no specific effects on fertility and a NOAEL of 720 mg/kg was derived.

For developmental toxicity, studies performed on animals via various administration routes did not demonstrate any teratogenic potential, but foetotoxicity and embryotoxicity (lethality and resorptions) were often observed, secondary to maternal toxicity (regenerative haemolytic anaemia). In human, epidemiological studies did not allow to draw any conclusion on EGBE, due to co-exposure with different glycol ethers and other chemicals, including known developmental toxins. Overall, it can be assumed that developmental toxicity due to EGBE in humans could not be expected without maternal toxicity.

3.2.3 Risk characterisation

The risk characterization performed in the RAR uses the minimal MOS approach and is performed for inhalation and dermal exposures of workers, consumers and humans exposed via the environment.

The SCHER agrees with the procedure used to convert the oral human NOAEL into a dermal NOAEL and an inhalatory NOAEC, as well as on the use of PBPK models to obtain internal dose in humans, thus lowering uncertainty factors related to toxicokinetic differences. The SCHER also agrees on the derivation of different minimal MOS, in which the higher sensitivity of rodents to the haemolytic effects induced by EGBE is taken into account.

The RAR indicates conclusions ii)[1] for all the considered occupational exposure scenarios regarding acute/repeated inhalation and dermal exposures (single and combined). The SCHER noticed that in some acute exposure scenarios the ratios MOS/mMOS is limited to 3-4: however, conclusions ii)[1] can be considered acceptable due to the overestimation of both inhalation and dermal exposures values. The same consideration applies to some dermal exposure scenarios (and the combined ones) for repeated dose toxicity.

Regarding consumer exposure, conclusion ii) is accepted in all cases, except for acute exposure following painting activity, where the MOS for inhalation (67) is very close to the mMOS value (50, derived by multiplying the default value for intraspecies difference for a factor of 5 to extrapolate from the LOAEC to the NOAEC in human). Therefore conclusion iii) is proposed.

The SCHER also supports conclusion ii) for exposures from the environment, due to the very high MOS values

4. LIST OF ABBREVIATIONS

BAA	2-Butoxy-Acetic Acid
DGBE	Di-ethylene glycol butyl ether
EASE	Estimation and Assessment of Substance Exposure
EGBE	2-butoxyethanol (synonym: Ethylene Glycol Butyl Ether)
(m)MOS	(minimal) Margin of Safety

LOAEC	Low Observed Adverse Effect Concentration
NOAEC	No Observed Adverse Effect Concentration
NOAEL	No Observed Adverse Effect Level
PBPK	Physiologically-Based PharmacoKinetics model
RAR	Risk Assessment Report
TGD	Technical Guidance Document

5. REFERENCES

Corley, R.A., Bormett, G.A. and Ghanayem, B.I., 1994. Of 2-Butoxyethanol and its major metabolite, butoxyacetic acid, in rats and humans. Toxicol. Appl. Pharmacol., 129**,** 61-79.

Corley RA, Markham DA, Banks C, Delorme P, Masterman A and Houle JM, 1997. PBPK and the dermal absorption of EGBE vapour by humans. Fund. Appl Toxicol., 39, 120- 130.

Lee KM, Dill JA, Chou BJ and Roycroft JH, 1998. PbPk model for chronic inhalation of EGBE. Tox. Appl. Pharmocol., 153, 211-226.