2-Butoxyethanol

A Review of the Current Toxicity Information

This summary was prepared in response to concerns regarding 2-BE in products. I am making this available to address the need for toxicological information regarding potential health damage from 2-BE in chemical treatments on an oil spill in the Gulf of Mexico. Additional scientific evidence regarding toxicity that has been published since this was written in December 2007 should be consulted.

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This summary does not contain any medical advice. It is a summary of the toxicological evidence regarding 2-BE, as provided in peer-reviewed scientific publications, government reviews, and company-provided literature on products.
This report was prepared on behalf of the City and County of San Francisco, Department of the Environment. This work was undertaken with the agreement that the work product could be, published, used and provided to the public as needed by Dr. Burns.

Conflict of Interest Statement
Dr. Burns states that she has no financial interest or other conflict of interest with respect to products containing 2-butoxyethanol or decisions made by the City and County of San Francisco regarding the use of the information contained in this report.
Summary

There is strong evidence regarding 2-BE with respect to impacts on two critical systems, the respiratory system, and the blood forming system. Both of these categories of effects may selectively impact some subpopulations, and may affect most people at some points in their lives. There is suggestive evidence regarding cancer and developmental/reproductive toxicity. Therefore, the use of safer alternatives is encouraged to the degree that is possible. For uses where other alternatives are not yet available, workers should use appropriate personal protective equipment only in areas with good ventilation, and after receiving clear hazard communication information, as required by law. It would be inadvisable to use products containing 2-BE in public areas or other places where fumes or mists could reach people who are not informed about the hazards and are not able to protect themselves from some important effects.

2-Butoxyethanol (2-BE) is commonly found in cleaning products, personal care and other consumer products, and in some paints, inks, and similar types of products. As a product used by city cleaning and maintenance employees, contractors, and other people who are working, studying, or carrying out activities in city-run programs (e.g., in schools, health care centers, day care or senior centers), it is of particular interest in cleaning products. While there are some limitations on the scientific data available on health effects of 2-BE in people, there is good evidence on some important effects.

It is clear that red blood cells are a target for 2-BE and this causes a series of other types of organ toxicity, including damage to the liver, kidney, spleen, and other organs. Populations at risk include people with related diseases or hereditary conditions (e.g., anemia, Sickle Cell Disease, liver or kidney disease) and women who are pregnant and therefore must produce red blood cells rapidly to support fetal growth and maintain their health.

2-BE is also a well-recognized irritant that affects the respiratory tract and the eyes. It can exacerbate asthma and many other respiratory diseases (e.g., emphysema, chronic obstructive pulmonary disease, upper and lower respiratory infections). Due to the prevalence of these conditions among the general public and working population, this is an important consideration in determining the advisability of using products that contain 2-BE. In the case of these effects, as well as any others, the severity of effects will vary depending on dose and the characteristics of individuals exposed to 2-BE.

Cancer studies in animals have found multiple types of cancer from exposure to 2-BE, but there is controversy regarding the application of these results to people. The US National Toxicology Program determined that there was some evidence of carcinogenicity in some species tested. The International Agency for Research on Cancer (IARC) found the study data in experimental animals was "limited". Studies of how cancer is induced also do not provide clear answers. There is also
limited evidence that 2-BE can cause genetic damage, which is related to both cancer and developmental damage.

Studies have found that 2-BE may cause damage to the fetus during development, including delayed bone formation and fetal death. Many chemicals in the glycol ether family are well established as causing severe harm during development. Damage to the reproductive system has also been observed, including reduced testicular size. These results are the subject of debate, and there is not consensus regarding the potential for harm at very low exposure levels.

There is controversy with respect to many of the important and potentially serious health effects that may be caused by 2-BE. A recent evaluation by the State of California concluded that reproductive toxicity should be the basis for controlling short-term high level exposures. In the absence of definitive information on this important health impact, a protective approach is recommended.

Note on resources:

The bibliography at the end of this report contains a large number of links to enable readers to directly access full text documents and articles. The information includes Material Safety Data Sheets that can be used to inform workers regarding the hazards of 2-BE, as well as some federal regulations relevant to this chemical.

Note on Technical Specifications:

The Department of the Environment, City and County of San Francisco provided "Technical Specifications for the Procurement of Janitorial Cleaners" on March 25, 2005. Those specifications cover 19 topics, and some topics are addressed by information provided in this report. Appendix B lists information that is relevant to those specifications.
I. Background

2-BE is a commonly used solvent with applications primarily in the product categories paints and coatings and cleaning products. There are minor additional uses (e.g., acrylic resin, photographic processing, firefighting foam). It is produced by specialty chemical manufacturers and the stock chemical (2-BE) is used by formulating manufacturers to generate most of the final products (e.g., paints and cleaning products). Links to Material Safety Data Sheets (MSDS), one with information on pure 2-BE and one for a cleaning product that contains dilute 2-BE as an ingredient, are provided Appendix A.

A primary function of 2-BE as a solvent in cleaning products is also the source of some of its toxic characteristics. As part of the family of glycol ethers and the subgroup of butyl glycol ethers, its properties can be assessed through consideration of its structural relatives, as well as the results of direct testing of 2-BE.

II. Exposure Assessment

Exposure assessment is not the focus of this report, but it is necessary to consider the potential routes of exposure, the likely levels of exposure, and who may be exposed to 2-BE in order to provide appropriate information on it's toxicity and potential health effects. This report focuses on the use of 2-BE in cleaning products and related maintenance products, which dictates to some degree the type of toxicity information to be considered. The use of the pure form of 2-BE is dangerous in some ways that are not relevant to cleaning products (e.g., flammability) and so is not considered here.

There are number of potential pathways of exposure to 2-BE when it is used in cleaning and other consumer and commercial products, including inhalation, skin (dermal) absorption, and ingestion. Each of these pathways is capable of causing the uptake of 2-BE into the body and therefore of causing the harmful effects associated with 2-BE (IRIS, 1999). The uptake into the body (dose) will vary by pathway and many individual factors.

**Inhalation.** 2-BE is typically used in liquid form, often as a spray. Both the spray itself and evaporation of the liquid form into the air can result in inhalation of 2-BE and other ingredients in a product. The amount inhaled will depend on the concentration in the product, the conditions of use, the ventilation where it is used, and individual factors such as breathing rate. The duration of exposure with respect to hours of use, number of days per week, and years used will all affect the amount of exposure, and consequently the potential health impacts.

**Dermal.** Exposure of the skin and eyes would also be expected in many situations. Products may be used without gloves and so hands and arms can be immersed in products containing 2-BE. The use of sprays and evaporation of products into the air result in differing amounts of dermal exposure. When a liquid sits on the skin, some of it can move through the skin into the circulating blood and lymphatic systems, moving throughout the body. It ultimately is able to circulate in the same way that occurs if it is ingested or inhaled, though dermal exposure is often
thought to be less likely to result in high levels of exposure due to the barriers that naturally occur in the skin.

Unfortunately, in the case of 2-BE and some ingredients it is formulated with in products, the solvent action makes it far easier for this chemical to move through the skin. It is capable of dissolving some of the protective barriers that exist. The amount of skin penetration will vary considerably depending on the formulation, the amount of time it is on the skin, and many individual characteristics such as skin thickness, any abrasions or other damage to the skin's outer layers, and the use of other products that reduce the skin's protective barrier properties.

**Ingestion.** Ingestion of 2-BE is less likely to occur as a part of normal product use in the products under consideration. It could occur if a spray were used near food or beverage preparation or consumption, or on surfaces as a part of cleaning and sanitizing.

**Variability in products.** There is very wide range of cleaning products containing 2-BE, and it is useful at the outset to clarify that different products may result in very different exposures and doses. For example, whiteboard cleaners are less likely to result in dermal exposure and absorption than liquid soaps. Dry cleaning solutions may impose heavy exposures on workers, but probably less on most members of the general public.

**Solvent action.** I have focused on the use of 2-BE in cleaning products, which confer some unique health hazards. It is likely that dermal contact will occur, and as a solvent, this chemical is readily absorbed through the skin, as noted above. That means that internal systemic circulation of the chemical can occur without inhalation or ingestion of the chemical. Inhaled doses from product use can occur simultaneously with dermal intake, and both routes must be considered in order to fully capture the potential for exposure and health effects. In addition, most cleaning products have multiple ingredients that are designed to act as solvents, emulsifiers, and in other ways degrade and remove debris. These additional chemicals will, in most cases, facilitate movement through the skin. The fat layer in the skin that acts as a barrier against absorbing chemicals in the environment will be undermined and penetrated by cleaning ingredients. The function of such cleaning agents is, after all, to move through and remove fat-based materials.

**Children.** While exposure of children may not be anticipated in most uses of cleaning products, it is relevant if cleaning products are used in a school or day care where children help with classroom cleanup. Skin exposure can occur when products are used when children are in close proximity. Young children have incompletely developed skin barriers, and so can absorb chemicals through their skin more easily than older children and adults. Additional susceptibilities of children are discussed below.

**Study Data - Nazaroff's work.** A recent evaluation of the 2-BE exposures for a professional domestic cleaners during various cleaning activities was carried out by Nazaroff et al (2006). The study provides evidence of exposures associated with various types of activities and product uses. For example, the highest exposures to 2-BE for a domestic cleaner were from cleaning counters and glass surfaces. Nazaroff evaluated a number of other work situations where 2-BE
was used and also provided results for two other chemicals of possible interest (formaldehyde and SOA) in the same report.

**Acute exposure - high levels over short time periods.** There are many serious hazards associated with high exposure levels, and as previously noted these are not all relevant when it is formulated in products in diluted form and when exposures are likely to be low (i.e., high intakes are unlikely). Because acute exposure to the pure form of this chemical is not under consideration here, I will not describe the toxic effects of that type of exposure. However, that information can be easily accessed in the online sources listed at the end of this report and is included in the summary in Appendix B.

**Protection from Exposure.** When exposure to 2-BE is anticipated in it’s pure form, for example, in manufacturing situations, protective clothing and other health and many safety precautions are required. Taking under consider the numerous uncertainties associated with 2-BE that are important, including it's potential to cause cancer and developmental damage, it is important that appropriate protective equipment and clothing be used when handling products containing 2-BE in order to minimize exposure. OSHA has specified what is required for high-level 2-BE exposures, and other agencies and organizations have also provided relevant information on this topic.

Appendix A contains links to documents that describe necessary protective clothing and equipment. It is advisable to review this and determine what steps will be required for the protection of workers using products that contain 2-BE, and what steps are prudent to protect the general public from exposure if it is necessary to continue using products that contain 2-BE.

**III. Potential Health Effects**

**A. Overview**

The range of effects caused by 2-BE in human and animal studies is extensive, including a number of effects on the developing fetus, (fetal death, poor fetal growth, and delayed bone formation, abnormal weight/growth patterns in the fetus), damage to the liver, spleen, renal, blood forming and urinary systems, and cancer (HSDB, 2007; CDC, 1999; IARC, 2006; NTP, 1985, 1989, 1993, and 2000; Tyl, 1984; Weir et al, 1987; Corthals, 2006).

**B. Cancer**

There have been a number of studies regarding the carcinogenic potential of 2-BE, and a very recent study on mechanisms of cancer induction. Animal studies of 2-BE found dose-related increases in hemangiosarcoma of the liver (male mice) and carcinoma of the forestomach (female mice). Combined benign and malignant cancers of the adrenal medulla were observed in female rats; however there were some difficulties associated with the study design. Benign and malignant cancers of the adrenal medulla were observed in female mice, but the evidence was not clear and the same effects were not seen in males (NTP, 2000).
The studies by the National Toxicology program (NTP, 2000) were well designed and the NTP determined that there was some evidence of carcinogenicity in male and female mice, equivocal evidence in female rats, and no evidence in male rats. This combination raises many questions, but does not provide definitive answers regarding cancer risks to humans.

The studies were completed in 1995 and since that time a number of studies were carried out to evaluate the mechanisms by which cancer was induced and it's relevant to humans. However, questions remain regarding the likelihood and nature of cancer risks that may exist. IARC hypothesized that stomach tumors were likely due to very high concentrations localized in that area and did not determine there was a clear link to human cancers in their final analysis. The IARC committee also determined that the liver cancers seen in experimental animals were unlikely to occur in humans. They have assigned 2-BE to a Group 3 status, stating there is “limited evidence” in animals and “inadequate evidence” in humans for determination of carcinogenicity (IARC, 2006).

A 2005 study by Klaunig and Kamendulis further clarified the mechanisms by which damage occurs and DNA synthesis is altered. That same year USEPA published a paper suggesting that there is "suggestive evidence for cancer" from animal studies but that further work is required (Gift, 2005).

A 2006 study by Corthals et al, found that chronic exposure to 2-BE increased liver hemangiosarcomas in male mice. The mechanism they described involves oxidative damage following red blood cell disintegration (hemolysis), iron deposition, activation of a specific type of cell in the liver, DNA damage in endothelial cells, and cell proliferation. Cell proliferation and hyperplasia commonly precede cancer. The authors suggest that these steps are necessary for the induction of hemangiosarcomas by 2-BE and that there is a threshold of exposure below which these do not occur (Corthals et al (2006).

These findings do not absolve the chemical as far as its carcinogenic potential goes, but rather explain why it has been difficult to obtain a straightforward or simple explanation of the means by which it causes some types of damage. The issue of whether or not there is an exposure threshold below which cancer cannot result from 2-BE exposure is unresolved. Relevant to this is the fact that variations in human response to chemical exposures arise from a myriad of factors. The heterogeneity of the human population with respect to genetics, health status, daily exposures to other hazards, and other factors alter our cancer susceptibility. Even if there were a threshold observed in animal studies, unlike homogeneous populations of rodents, the diversity of the human population may make it impossible to determine a threshold below which the human population will not be at risk.
C. Genotoxicity

Genotoxicity is important with respect to both cancer and developmental toxicity. Damage to genetic material can occur in body cells (somatic) and/or in reproductive cells, and both can lead to cancer and damage to future generations. So it is important to consider whether 2-BE has the capacity to damage DNA directly or alter its function.

Most studies of 2-BE have found it is not genotoxic. There are many mechanisms by which DNA damage can occur, and by which the expression of DNA's control over cellular function can be altered. Consequently, it is important to consider a wide range of genotoxicity tests in order to insure that mechanisms by which a chemical can cause genetic damage are fully evaluated (to the degree possible given the current state of science).

A 1999 report by Duerksen-Hughes et al considered previous test results that had been obtained through the use of new genetic tests for 25 chemicals, including 2-BE. The study reported the negative results obtained for both the older standard genetic tests (e.g., Ames) and for a newer P53-induction test. They also reported that there were positive results in a Syrian Hamster embryo test, and that in vivo (in live animal) tests some positive results were obtained (Duerksen-Hughes et al, 1999). This suggests that 2-BE might cause genetic damage by mechanisms that were not easily identified in traditional tests.

The Corthals et al (2006) study cited above found evidence that 2-BE and related metabolites do not directly cause DNA damage. This is important in evaluating the carcinogenic potential of a chemical. The issue of direct action speaks to the problem that we see with many chemicals which are capable of acting indirectly to modify how DNA functions. This can occur through many mechanisms. Whether direct or indirect acting, evidence of alterations in DNA function is an important aspect of determining whether this or other chemicals are likely to be carcinogenic at low doses, and how they will be managed in the regulatory context.

Specific challenges are raised when chemicals act indirectly via complex systems (e.g., damage to the hematopoietic system, leading to macrophage activation, and subsequent DNA damage, as described above). Most physiological systems have a “buffering” capacity that allows them to address minor perturbations that occur in the body. We have what are often referred to as “homeostatic” mechanisms - those that maintain blood pressure, body temperature, and other basic functions. Though less well understood, most organ systems have similar mechanisms to maintain a normal functional level. That allows the body to withstand a number of challenges that routinely occur.

Unfortunately, a large proportion of people exist for whom these mechanisms do not work well at various times during their lives and so are less able to safely handle exposure to carcinogens. Increased susceptibility may be due to illness, external stresses on their systems (e.g., other hazardous exposures occurring simultaneously), and life events (e.g., pregnancy, early phases of development). Consequently, what “should” happen to protect people during variations in function, don’t always do so sufficiently over the entire lifespan.
In addition, there are many people with genetic or other alterations that are never or no longer able to adequately deal with stresses on various systems. Examples include individuals with one of the many heritable liver/metabolic disorders and those who have had liver damage through accidents, disease, problems with transfusions, etc. These can be considered a special class of “susceptible subpopulations” with respect to 2-BE and liver damage. They are likely to be at greater risk for hemangiosarcoma than those with normal liver function.

Whether or not 2-BE places people with various susceptibilities at greater risk of cancer has not been determined. Some evidence exists that it does not cause people with hereditary spherocytic or sickle cell disease to suffer adverse effects (Udden, 1994, Udden and Patton, 1994). However, that conclusion was drawn by authors after a 4 hour exposure, which does not represent well an ongoing exposure that could occur in a workplace, school, or other public service situation.

Genotoxicity, via direct or indirect actions, is also relevant to considerations of heritable birth defects and damage during development. The lack of direct interactions suggests that there would not likely be an impact on the heritable (reproductive) cells. However, toxicity to a mother who is especially susceptible to liver damage, or to a fetus who has inherited liver function abnormalities could result in harm at far lower exposures than would be expected among women or a fetus without such susceptibilities.

For all of the reasons above, we cannot assume knowledge of a “safe” level of exposure to 2-BE without careful sufficient scientific evidence and careful review of the relationship between various known human liver conditions and the mechanisms by which 2-BE causes damage. In the absence of that information, we must assume either that we are not able to protect all of the members of the population, or that a very substantial safety factor - margin of error assumption - must be incorporated in order to protect against harm. This consideration applies to the information provided in subsequent sections as well.

D. Chronic Toxicity

Studies of 2-BE continue to shed light on the effects and underlying mechanisms of the different types of damage caused by 2-BE (see compilation of studies in CDC (1998), National Toxicology Program’s technical report in 2000 which provided considerable detail from lifetime studies in experimental animals, and numerous papers published up through Ramot (2007)).

Chronic studies in humans and experimental animals have found that 2-BE causes damage to red blood cells. The hematopoietic system is a primary target of 2-BE and exposure can result in anemia, the more disease - severe hemolytic anemia, and microvascular thrombosis. There is scientific controversy regarding the degree of correspondence between experimental animals and humans with respect to their sensitivity to 2-BE, as reflected in the debate regarding its carcinogenic status (indicated above). The issues regarding red blood cell damage and the sequence of additional damage that results from that is more a question of degree than of whether such damage occurs. Effects are seen in both human populations and in animals, but there are
differences both among animal species tested and between humans and animals that complicate interpretation of the toxicological data on 2-BE (e.g., results reported in NTP, 2000).

The damage that 2-BE causes to red blood cells has serious secondary consequences throughout the body. The widespread thrombosis that is caused by the release of red blood cell constituents and other pathological actions at the cellular level resembles sickle cell disease and beta-thalassemia (Ramot, 2007). Recent studies also suggest that there may be differences in susceptibility over the lifespan, based on observations of such differences in animals (Ramot, 2007).

The deposition of iron from the destroyed red blood cells can cause damage to the liver, and that is hypothesized to be one of the mechanisms of cancer induction, as noted above (Klaunig and Kamendulis (2005). Liver damage compromises many other systems in the body, and adequate liver function is essential to life. Independent of cancer concerns, liver damage is a serious and potentially lethal medical consequence.

People will be at greater risk from 2-BE exposure if they have certain characteristics. These include pre-existing liver disease, predispositions to liver disease for genetic or other reasons, and exposures to additional liver toxins in addition to 2-BE (e.g., many industrial chemicals fall into this category, as does alcohol).

Anemia that results from 2-BE's damage to red blood cells ranges from mild to very severe. Anemia causes a variety of problems throughout the body, including some symptoms that may be difficult to identify such as tiredness and weakness. Anemia during pregnancy is especially dangerous and can affect both the mother and the fetus. Anemia during some disease states (e.g., cancer) is also very dangerous and can undermine recovery. Individual susceptibility to anemia varies from one individual to the next and over the lifespan.

The subchronic study by NTP evaluated localized damage to various organs. Thrombosis that resulted from destruction of red blood cells caused damage to a variety of tissues. Thrombosis was observed in the lung, liver, and heart and was related to infarction that occurred in the vertebrae. In both species of rodents tested, the females suffered greater damage than the males (NTP, 2000).

Other serious damaging effects of 2-BE that were observed in the subchronic NTP studies included damage to the kidneys (renal tubule degeneration), atrophy of the spleen, thymus and lymph nodes, and degeneration of the testis (NTP, 2000).

Based on the nature of the damage that occurred in animal studies, it is possible to hypothesize that certain human population subgroups would be at greater risk from exposure to 2-BE than the general population. Their conditions may be aggravated, or conditions may be prompted to occur in those with susceptibilities to diseases in certain organ systems. Based on the chronic toxicity tests available on 2-BE, those at special risk could include people who have pre-existing circulatory system or blood clotting disorders or a genetic predisposition to such diseases, those with kidney, spleen, thymus or lymphatic system disorders or susceptibilities, and those with
testicular pathology. This is in addition to the already-mentioned susceptibilities of those with blood-related diseases or conditions.

E. Irritant Effects

2-BE is an irritant and can cause damage to the eyes and respiratory tract (California OEHHA, 1999; IARC, 2006). Irritants can trigger asthmatic episodes in people with asthma, and in some cases (e.g., for asthmatics who have moderate or severe asthma), this can require medication or hospitalization. Given the large percentage of asthmatic children and the growing number of adults with asthma, this is a very serious consideration when products containing 2-BE may result in the exposure of workers or the general public who have asthma.

Irritant effects also pose risks for people with chronic obstructive pulmonary disease, emphysema, and other respiratory diseases and conditions. Irritant effects can impact the eyes which causes difficulty for people with various ocular conditions. In some cases irritant effects can be harmful to the skin, depending on the susceptibility of the individual to low levels likely to be found in cleaning products (e.g., to people with dermatitis).

F. Developmental and Reproductive System Toxicity

Developmental toxicity studies of 2-BE in experimental animals resulted in a number of adverse effects, including delayed skeletal formation (ossification) and intrauterine deaths (Tyl et al, 1994, Ghanayem et al, 1992). Due to the observance of maternal toxicity, some have argued that the effects are not relevant, but merely result from maternal toxicity. That has not been clearly established by follow up studies to adequately sort out this issue.

In reproductive studies, toxicity was observed in male experimental animals that were found to have reduced testicular size (Lamb, 1997). Reduced fertility was observed along with lower body weight of offspring in the second generation and increased liver and kidney weights. The summary information indicated that there was not a clear "no effect" level, and that both males and females were affected. Reduced intake of food and water may have played a role in some effects observed (Lamb, 1997), but is unlikely to have been the cause of the abnormal and disproportionate growth of various organs.

2-BE belongs to a family of structurally similar chemicals, the glycol ethers, that include chemicals known to be among the most toxic to the fetus. The State of California has provided information regarding glycol ethers, including listing many as reproductive toxins (California EPA, 2007).

California's OEHHA recommended an exposure limit for 2-BE based on its reproductive toxicity and defended their decision against industry comments as follows:

"Based on reevaluation of the literature, the key reference and the endpoint for the REL for EGBE has changed. The most sensitive endpoint for EGBE is reproductive
toxicity. The REL is based on reduced gravid uterine weight, reduction in total fetuses, fewer viable fetuses, increased maternal deaths, increased spontaneous abortions, and decreased body weight in rabbits, as reported by Tyl et al. (1984)."

Their comments are provided in their entirety in Appendix B, Section B.

Due to the developmental and reproductive toxicity that was observed in experimental animals, as discussed above, it is prudent to consider women who are or may become pregnant to be at higher risk. The reproductive toxicity studies indicate the potential for harm, and taken together with the developmental toxicity studies indicate the need for a protective approach to individuals who are pregnant or men or women who may wish to have children in the future.

G. Sensitive Subpopulations

Sensitive populations have been described above following discussions of the various categories of health effects. They include individuals with It is notable that the State of California has determined that those with preexisting neurological or kidney conditions might be more sensitive than the general population (California OEHHA, 1999).

IV. Conclusions

2-BE is a well-recognized irritant and red blood cell toxicant. It may also cause a wide spectrum of damage to various organ systems and has some evidence of carcinogenicity. The likelihood that it can cause developmental/reproductive toxicity is substantial, based on available studies and on the importance of red blood cell production is during pregnancy and early fetal development. Exposures that occur as the result of the use of cleaning products are therefore of concern.

If safer alternatives exist, the use of 2-BE should be avoided. If products containing 2-BE are used due to a lack of alternatives, it is important to provide comprehensive health and safety information to workers regarding potential health effects. Appendix A contains examples. Suppliers must provide an MSDS on request - often requiring supplemental information. Workers should receive adequate personal protective equipment to minimize exposure. And it is strongly recommended that individuals be allowed to opt out of using 2-BE based on concerns or potential susceptibility to the effects of 2-BE¹.

The use of products containing 2-BE is highly questionable in areas where the general public may be exposed because it is not possible to adequately inform the public regarding the potential hazards or to identify and remove individuals with greater susceptibility.

¹ A number of susceptible subgroups were identified throughout the text.
Bibliography


Hazardous Substances Data Bank (HSDB). Extracted online 2007. Accessible at: http://toxnet.nlm.nih.gov/cgi-bin/sis/search/r?dbs+hsdb:@term+@rn+111-76-2 Note that some of the information is outdated. See also access via NTP at: http://ntp.niehs.nih.gov/go/25759 for HSDB information most relevant to a health evaluation.


National Trade Data Bank (NTDB). Monobutyl ethers of mono or di-ethylene glycols. National Trade Data Bank: The Export Connection.


NTP. 1989. Teratologic evaluation of ethylene glycol monobutyl ether (CAS no. 111 76 2) administered to Fischer-344 Rats on either gestational days 9 through 11 or days 11 through 13. Abstract at: http://ntp.niehs.nih.gov/go/7776


Appendix A. Examples of Material Safety Data Sheets and Similar Information Products

The information conveyed in fact sheets and material safety data sheets (MSDS) includes basic health hazard data. I have provided links below to two MSDSs as examples. One is for 2-BE as an isolated chemical (i.e., very potent - not diluted) and another for a product that contains a substantial amount of 2-BE but is diluted by other ingredients. While these provide some useful information, summaries and MSDS sheets vary widely, especially with respect to the provision of information regarding potential reproductive and carcinogenic effects.

2-BE as a pure product, by Mallinckrodt Baker, Inc. Phillipsburg, NJ
http://www.jtbaker.com/msds/englishhtml/b6100.htm


The Western Regional Pollution Prevention Network also provides a good summary of information on 2-BE at: http://www.wrppn.org/janitorial/tools/butoxy.htm This is based substantially on the New Jersey Hazardous Substances Fact Sheet for 2-BE that is available at: http://nj.gov/health/eoh/rtkweb/documents/fs/0275.pdf

Other listings for the pure chemical and products it is contained in, and links to a wide spectrum of information on the chemical and products is accessible via the National Library of Medicine's website on Household Products: http://householdproducts.nlm.nih.gov/cgi-bin/household/brands?tbl=chem&id=45
Appendix B. Information Relevant to the Technical Specifications for the Procurement of Janitorial Cleaners adopted by the City and County of San Francisco on March 25, 2005.

The specifications regarding janitorial cleaners include the topics listed below. These topics were covered in this report and so the information summarized below to simplify a comparison of specifications to the characteristics of 2-BE.

The product itself will have different characteristics than 2-BE because 2-BE would be one of many ingredients. That will substantially dilute the effects of 2-BE. Consequently, the information below is provided to inform the reader about the general impact that inclusion of 2-BE as an ingredient will have on a product as one of many ingredients (e.g., potentially increasing its irritant effect).

The information that follows the technical specifications is expected to be directly relevant to decisions regarding this chemical because it reflects decisions by the State of California's Office of Environmental Health Hazard Assessment (OEHHA). Section A describes the basis for an exposure limit, and Section B contains responses to comments regarding OEHHA's decisions and clarification of the importance of protecting against reproductive toxicity for this chemical.

The information below was obtained from these sources: HSDB, 2007; CDC, 1999; the summary information provided directly below this section (California OEHHA), and the documents provided via links in Appendix A.

____________________________________________________________________

1. Toxic Compounds - Acute Toxicity: 0.5 to 1.4 mL/kg; OSHA PEL is 50 parts per million; NIOSH REL is 5 ppm; NIOSH immediately dangerous to life or health concentration (ISLH): 700 ppm.

2. Carcinogens and Reprotoxins: California's REL for 2-BE is based on reproductive toxicity, as indicated in the "Response to Comments" from OEHHA below (Section B).

3. Eye and Skin Irritation: Yes

4. Skin Sensitization: unknown

5. Combustibility: Flashpoint is 144 F, and autoignition occurs at 460 F

____________________________________________________________________
A. Determination of Acute Reference Exposure Levels for Airborne Toxicants: Acute Toxicity Summary: Ethylene Glycol Monobutyl Ether.


Available online at: http://www.oehha.ca.gov/air/acute_rels/pdf/111762A.pdf

C - 110- Ethylene Glycol Monobutyl Ether
(2-butoxyethanol, butyl cellosolve, butyl glycol)

ACUTE TOXICITY SUMMARY
CAS Registry Number: 111-76-2

I. Acute Toxicity Summary (for a 1-hour exposure)

Inhalation reference exposure level 14,000 mg/m³
Critical effect(s) irritation
Hazard Index target(s) Respiratory System

II. Physical and Chemical Properties (HSDB, 1994 except as noted)

Description colorless liquid
Molecular formula C₆H₁₄O₂
Molecular weight 118.20
Density 0.90 g/cm³ @ 20°C
Boiling point 171°C
Melting point -70°C
Vapor pressure 0.76 mm Hg @ 20°C
Flashpoint unknown
Explosive limits unknown
Solubility soluble in water, acetone, benzene, carbon tetrachloride, ethyl ether; miscible with ketones, ethers, alcohols and halogenated hydrocarbons
Odor threshold 0.10 ppm (geometric mean) (AIHA, 1989)
Odor description sweet, ester-like, musty (AIHA, 1989)
Metabolites butoxyacetic acid (Johanson et al., 1986)
Conversion factor 1 ppm = 4.84 mg/m³ @ 25°C

III. Major Uses or Sources

Ethylene glycol monobutyl ether (EGBE) is used as a coupling agent to stabilize immiscible ingredients in metal cleaners, textile lubricants, and cutting oils (HSDB, 1994). It is also used as a solvent for nitrocellulose resins, spray lacquers, enamels, and varnish removers. EGBE is also found in hydraulic fluids.
IV. Acute Toxicity to Humans

Two adult male volunteers were exposed to 113 ppm (550 mg/m³) EGBE for 4 hours. Eye, nose and throat irritation, taste disturbances, and headache and nausea were reported (Carpenter et al., 1956). Erythrocyte osmotic fragility and urinalysis were normal in the subjects during and after exposure. In this study, 8-hour exposures at the same concentrations resulted in similar reports of discomfort.

Four volunteers were exposed either mouth-only or skin-only, by a mouthpiece or a respirator in a chamber, to 50 ppm EGBE for 2 hours (Johanson and Boman, 1991). Capillary blood samples were taken at regular intervals to determine rate of uptake from dermal and inhalation (mouthonly) exposure. The experiment was done under both normal and raised humidity conditions. The authors concluded that dermal uptake of EGBE from air is approximately four times greater than respiratory uptake. The authors also note that dermal uptake increased with air temperature and humidity.

Seven healthy male adults were exposed to 20 ppm (100 mg/m³) EGBE in a chamber experiment designed to assess pulmonary uptake and metabolism of EGBE. Butoxyacetic acid was the primary metabolite found in the urine (Johanson et al., 1986). The authors report that 57% of the inhaled dose was absorbed in the respiratory tract. The authors report that none of the subjects complained or showed any adverse effects from exposure for 2 hours to 20 ppm EGBE.

Although increased erythrocyte fragility has been observed in rodents following exposure to EGBE (Carpenter et al., 1956), recent studies found no increase in the fragility of human erythrocytes taken from normal and susceptible individuals (persons with hereditary spherocytosis or sickle cell disease and older persons) following a 4-hour incubation with butoxyacetic acid (Udden, 1994; Udden and Patton, 1994).

Predisposing Conditions for EGBE Toxicity
Medical: Persons with preexisting neurological, blood or kidney conditions might be more sensitive (Reprotext, 1999).

V. Acute Toxicity to Laboratory Animals

A 7-hour LC50 for mice was reported as 700 ppm (3,000 mg/m³) EGBE (Werner et al., 1943). Severe hemoglobinuria was observed; hepatic focal necrosis and splenic lymphoid hyperplasia were noted at necropsy. An 8-hour LC50 in rats was reported as 564 ppm (2,800 mg/m³) EGBE (Pozzani et al., 1959).

No mortality or other clinical signs of toxicity were observed in 5 male and 5 female guinea pigs exposed to 691 or 633 ppm EGBE, respectively, for one hour (Nachreiner, 1994). Further, no signs of toxicity were observed during the 14-day post-exposure period or at necropsy.

Rats were exposed to 867, 523, or 202 ppm EGBE for four hours (Dodd et al., 1983). Exposure was lethal to all animals in the 867 ppm group and to 2/6 males and 3/6 females in the 523 ppm group. No deaths were observed in the 202 ppm EGBE exposure group. Rats exposed to 867 ppm exhibited loss of coordination and shallow breathing and had a red discharge around the urogenital area. Red-stained fluid in the urinary bladder and enlarged and discolored kidneys were observed at necropsy of the animals that died during or following exposure to 867 or 523 ppm EGBE.

Increased erythrocyte fragility was observed in rats exposed for 4 hours to 62 ppm (300 mg/m³) EGBE (Carpenter et al., 1956). No significant increase in erythrocyte fragility was observed following a 4-hour exposure to 32 ppm (150 mg/m³) EGBE.

Corley et al. (1994) developed a physiologically based pharmacokinetic model to describe in rats and humans the disposition of EGBE and its major metabolite, 2-butoxyacetic acid (BAA); BAA is the agent that causes lysis of red blood cells. The model predicted that rats metabolize EGBE and eliminate BAA faster per kg body weight than humans do. The balance of the two processes in addition to physiological differences between species resulted in higher predicted peak blood concentrations for rats as well as total areas under the blood concentration (AUC) time
curves for BAA. The species differences in kinetics coupled with the fact that human blood is significantly less susceptible than rat blood (and mouse blood and probably rabbit blood) to the hemolytic effects of BAA (Udden et al., 1994a,b) indicate that there is less risk for hemolysis in humans as a result of exposure to EGBE than predicted solely by standard rat toxicity studies.

VI. Reproductive or Developmental Toxicity

No studies on the developmental and reproductive toxicity of EGBE in humans were located in the literature.

Pregnant rats were exposed to 0, 25, 50, 100, or 200 ppm EGBE 6 hours per day on days 6-15 of gestation (Tyl et al., 1984). A significant increase in the incidence of delayed skeletal ossification was observed in the offspring of rats exposed to 100 or 200 ppm EGBE. Maternal toxicity, as indicated by decreased body weight gain, decreased food consumption, and significantly decreased erythrocyte indices, was observed in rats exposed to 100 or 200 ppm EGBE. It is not clear whether the reported delayed ossification effects indicate distinct developmental toxicity since there was concurrent maternal toxicity (RCHAS, 1994).

The same study exposed pregnant rabbits to 0, 25, 50, 100, or 200 ppm EGBE 6 hours per day on days 6-18 of gestation. Treatment-related increases in maternal deaths, spontaneous abortions, and decreased body weight were observed in does exposed to 200 ppm EGBE. Embryotoxicity, indicated by reduced gravid uterine weight and a concomitant reduction in total and viable fetuses, was observed at 200 ppm. Hematological parameters in the does were normal. However, rabbit erythrocytes resemble rat erythrocytes and are therefore also sensitive to the hemolytic effects of the reactive metabolite of EGBE (Ghanayem et al., 1992). The study indicates a LOAEL of 200 ppm and a NOAEL of 100 ppm for maternal and embryotoxicity in rabbits. EGBE has not been listed as a developmental or reproductive toxicant under Proposition 65.

VII. Derivation of Acute Reference Exposure Level and Other Severity Levels

(for a 1-hour exposure)

Reference Exposure Level (protective against mild effects): 14,000 mg/m³

Study Carpenter et al., 1956; Johanson et al., 1986

Study population human volunteers 2 in Carpenter; 7 in Johanson et al.)

Exposure method inhalation of 113 ppm for 4 hours (2 men) in Carpenter et al. (1956); inhalation of 20 ppm in Johanson et al. (1986)

Critical effects mucous membrane irritation of the nose and eyes

LOAEL 113 ppm

NOAEL 20 ppm for 2 hours

Exposure duration 2 or 4 hours

Equivalent 1-hour concentration 28 ppm (202 * 2 hours = C2 * 1 hour))

LOAEL uncertainty factor 1

Interspecies uncertainty factor 1
Intraspecies uncertainty factor 10

Cumulative uncertainty factor 10

Reference Exposure Level 2.8 ppm (14 mg/m³; 14,000 mg/m³)

Two human volunteers were exposed to 113 ppm EGBE for 4 hours (Carpenter et al., 1956). Symptoms observed included nasal and ocular irritation, disagreeable metallic taste, and a slight increase in nasal mucus discharge. The time to onset of symptoms was not specified; thus no time adjustment was made. Volunteers exposed to 98 ppm for 8 hours with a 30-minute break and 3 volunteers exposed to 195 ppm for 8 hours showed similar symptoms. The 3 exposed to the highest level agreed that it was too high for comfort. In Johansen et al. (1986) 7 healthy adults were exposed to 20 ppm in a study designed to look at the toxicokinetics of EGBE. The authors report that the subjects did not complain of adverse effects. Thus, this level can be identified as a freestanding NOAEL.

Level protective against severe adverse effects

No recommendation is made due to the limitations of the database.

Tyl et al. (1984) exposed pregnant rabbits to 0, 25, 50, 100, or 200 ppm EGBE 6 hours per day on days 6-18 of gestation. Treatment-related increases in maternal deaths, spontaneous abortions, and decreased body weight were observed in does exposed to 200 ppm EGBE. Embryotoxicity, indicated by reduced gravid uterine weight and a concomitant reduction in total and viable fetuses, was observed at 200 ppm. The study indicates a LOAEL of 200 ppm and a NOAEL of 100 ppm for maternal and embryotoxicity in rabbits. Rabbit erythrocytes resemble rat erythrocytes and are therefore also sensitive to the hemolytic effects of the reactive metabolite of EGBE (Ghanayem et al., 1992). Hematologic parameters in the does were normal but there was evidence in their cages of hematuria. Therefore, it is not clear if the reproductive and fetal toxicity were secondary to hematological effects. No adverse effects to does or fetuses were observed following exposure to 0, 25, 50 or 100 ppm EGBE. This study indicates a LOAEL of 200 ppm and a NOAEL of 100 ppm for maternal toxicity and embryotoxicity in rabbits. The pharmacokinetic model of Corley et al. (1994), as well as other evidence in humans and incubated human erythrocytes, indicates that that there is considerably less risk for hemolysis in humans as a result of exposure to EGBE than predicted solely by standard animal toxicity studies.

Level Protective Against Life-threatening Effects

No recommendation is made due to the limitations of the database.

Data on lethal effects of EGBE in species resistant to the hemolytic effects of EGBE were not available other than a 1-hour free-standing NOAEL of 633-691 ppm in guinea pigs (5 per sex) (Nachreiner, 1994). The only lethality study providing dose-response data had been conducted in mice (Werner et al., 1943). Both rats and mice have been shown to be sensitive to hemolysis following EGBE exposure. This effect is not observed in humans, including sensitive human subpopulations such as the elderly or those persons with sickle cell disease or hereditary spherocytosis (Udden and Patton, 1994; Udden, 1994). Therefore, the use of mouse lethality data may not accurately reflect the risk of potentially lethal effects in humans following EGBE exposure.

VIII. References


Corley RA, Bormett GA, Ghanayem BI. Physiologically based pharmacokinetics of


Pozzani UC, Weil CS, Carpenter CP. The toxicological basis of threshold limit values: 5. The experimental inhalation of vapor mixtures by rats, with notes upon the relationship between single dose inhalation and single dose oral data. Ind Hyg Assoc (no volume #) 1959:364-369.

(RCHAS) Reproductive and Cancer Hazard Assessment Section. Memorandum on ethylene glycol monobutyl ether reproductive toxicity to George Alexeeff, Air Toxicology and Epidemiology Section (ATES) from Jim Donald, Reproductive Toxicology Unit. July 20, 1994.


Tyl RW, Millicovsky G, Dodd DE, Pritts IM, France KA, Fischer LC. Teratologic evaluation of ethylene glycol monobutyl ether in Fischer 344 rats and New Zealand white rabbits following inhalation exposure. Environ Health Perspect 1984;57:47-68.


B. California OEHHA Reference Exposure Levels: Responses to Comments

Source of comments and responses:
http://www.oehha.ca.gov/air/acute_rels/response4_3.html#egep

Ethylene Glycol Ethers Panel - select comments related to EGBE:

Comment: The Panel wishes to bring to your attention toxicity information concerning ethylene glycol butyl ether that indicates the proposed acute toxicity reference exposure level (REL) for this chemical should be increased. First, a NOAEL irritation level has recently been demonstrated in humans by Johanson and Boman, who exposed volunteers to 50 ppm for two hours without reporting any irritation (or any systemic toxicity). "Percutaneous Absorption of 2-Butoxyethanol Vapour in Human Subjects," Br. J. Ind. Medicine, 48:788-792 (1991). Second, an uncertainty factor of 10 for acute effects in potentially sensitive individuals is unduly large. The OSHA PEL for EGBE has for many years been 50 ppm (although this was reduced to conform to the ACGIH TLV of 25 ppm for a few years). No reports of irritation have occurred under these limits.

Response: Based on reevaluation of the literature, the key reference and the endpoint for the REL for EGBE has changed. The most sensitive endpoint for EGBE is reproductive toxicity. The REL is based on reduced gravid uterine weight, reduction in total fetuses, fewer viable fetuses, increased maternal deaths, increased spontaneous abortions, and decreased body weight in rabbits, as reported by Tyl et al. (1984). Human sensory irritation data for EGBE identify NOAELs and LOAELs that are not protective of the potential reproductive toxicity described above.

Comment: Although the Level II and Level III findings will not be employed by California (given the existence of a Level I value), both values fail to reflect the substantial database indicating man is much less susceptible to hemolytic effects than rats and mice. Given these failings, we urge OEHHA not to issue Level II or Level III RELs for EGBE.

Response: The rat LOAEL was originally used as it was the lowest LOAEL reported in the study. However, to more accurately reflect data indicating that rats and mice are more sensitive to hemolysis following EGBE exposure, the severe adverse effect level has been revised.

While it is well characterized that rats and mice are more sensitive than humans to the hemolytic effects of EGBE, toxicity has been shown in species that did not exhibit signs of hemolysis. Tyl et al. (1984) reported rabbit data indicating the occurrence of embryotoxicity and maternal toxicity unrelated to hemolysis. Data on embryotoxicity and maternal toxicity, while not
synonymous with developmental toxicity, provides compelling evidence of non-hemolysis toxicity. For the previous reasons, data on toxicity of EGBE in pregnant rabbits provide the basis for the revised Level II.

Although Udden et al. (1994) clearly demonstrated that human subpopulations with hemolytic disorders were not more sensitive to the hemolytic effects of EGBE, the variability in human responses has not been completely characterized. Because the mechanism for rabbit maternal toxicity and embryotoxicity is unclear and because the true range of human responses is uncharacterized, an UF of 10 is used.

The life threatening effect level has been withdrawn and lethality data from a guinea pig, a species less sensitive than the rat to EGBE, has been added to the body of the summary.

References


Tyl RW, Millicovsky G, Dodd DE, Pritts IM, France KA, Fischer LC. Teratologic evaluation of ethylene glycol monobutyl ether in Fischer 344 rats and New Zealand white rabbits following inhalation exposure. Environ Health Perspect 1984;57:47-68.

