

# Defining maximum levels of higher alcohols in alcoholic beverages and surrogate alcohol products

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Received 13 September 2007

Available online 16 January 2008

## Abstract

Higher alcohols occur naturally in alcoholic beverages as by-products of alcoholic fermentation. Recently, concerns have been raised about the levels of higher alcohols in surrogate alcohol (i.e., illicit or home-produced alcoholic beverages) that might lead to an increased incidence of liver diseases in regions where there is a high consumption of such beverages. In contrast, higher alcohols are generally regarded as important flavour compounds, so that European legislation even demands minimum contents in certain spirits. In the current study we review the scientific literature on the toxicity of higher alcohols and estimate tolerable concentrations in alcoholic beverages.

On the assumption that an adult consumes  $4 \times 25$  ml of a drink containing 40% vol alcohol, the maximum tolerable concentrations of 1-propanol, 1-butanol, 2-butanol, isobutanol, isoamyl alcohol and 1-hexanol in such a drink would range between 228 and 3325 g/hl of pure alcohol. A reasonable preliminary guideline level would be 1000 g/hl of pure alcohol for the sum of all higher alcohols. This level is higher than the concentrations usually found in both legal alcoholic beverages and surrogate alcohols, so that we conclude that scientific data are lacking so far to consider higher alcohols as a likely cause for the adverse effects of surrogate alcohol. The limitations of our study include the inadequate toxicological data base leading to uncertainties during the extrapolation of toxicological data between the different alcohols, as well as unknown interactions between the different higher alcohols and ethanol.

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**Keywords:** Higher alcohols; Methanol; Ethanol; Propanol; Butanol; Alcoholic beverages; Fusel oil; Surrogate alcohol

## 1. Introduction

Alcohols with more than two carbon atoms are commonly called higher or fusel alcohols. In the 19th century, the predominant opinion was that higher alcohols were a contamination of alcoholic beverages derived as metabolites from bacterial spoilage (Huckenbeck and Bonte, 2003). However, since Ehrlich's work at the beginning of the 20th century it has been known that higher alcohols are formed by yeast metabolism from amino acids and therefore are normal constituents naturally found in all alcoholic beverages derived from alcohol of agricultural origin (Ehrlich, 1906, 1907, 1913). In contrast, methanol is formed from pectines and not from yeast metabolism (von Fellenberg, 1914). An

excellent evaluation of the tolerable concentration of methanol in alcoholic beverages is available in the literature (Paine and Dayan, 2001). Law already limits the methanol content in alcoholic beverages (European Council, 1989). Therefore, methanol will not be discussed in this article, which instead concentrates on higher alcohols for which there is no similar information.

The major higher alcohols found in alcoholic beverages are 1-propanol (*n*-propyl alcohol), 1-butanol (*n*-butyl alcohol), 2-butanol (*sec.* butyl alcohol), iso-butanol (2-methyl-1-propanol) and isoamyl alcohol (3-methyl-1-butanol). An interesting discrepancy should be noted about the evaluation of higher alcohols in alcoholic beverages:

On the one hand, higher alcohols are treated as important flavour compounds. For example, they commonly account for about 50% of the aromatic constituents of wine, excluding ethanol (Jackson, 2000). In food legisla-

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tion, the content of higher alcohols in alcoholic beverages is generally not seen as toxicologically relevant. For example, the Joint FAO/WHO Expert Committee on Food Additives included higher alcohols (1-propanol, 1-butanol, isobutanol) in the functional class ‘flavouring agent’ and commented that there was no safety concern at current levels of intake (JECFA, 1997). For certain groups of spirits, the European Union even demands a minimum volatile substance content (i.e., the quantity of volatile substances, mainly higher alcohols, other than ethanol and methanol). For example, brandy, fruit spirits or rum must have at least a content of volatile substances of 125, 200 or 225 g/hl of pure alcohol, respectively (European Council, 1989).

On the other hand, in previous studies of surrogate alcohol a number of authors attributed the possible higher toxicity of this group of illegal or home-produced alcohol to its content of higher alcohols (Lachenmeier et al., 2007). For example, compared to consumers of mainly licit alcohol, consumers of home made ‘country liquor’ in India have been reported to have higher rates of alcoholic liver disease (Narawane et al., 1998), and an animal study on rats suggests that “toddy” (an Indian country liquor) had increased toxicity compared to the same dose of pure ethanol (Lal et al., 2001). McKee et al. (2005) concluded from a study of Russian samogons (the Russian name for illegally home-distilled alcoholic beverages) that they contain aliphatic alcohol congeners at “toxicologically relevant levels”. Lang et al. (2006) went so far as to conclude that illegal products in Estonia contain “toxic long chain alcohols”. Regrettably, the latter studies did not state how they derived this conclusion or what they consider a “relevant” or “toxic” level.

In summary, higher alcohols have been treated as “generally recognized as safe” or as “toxicologically relevant”. Accordingly, our study tries to answer the question of the maximum tolerable level of this important substance class in alcoholic beverages.

## 2. Methods

In order to derive such maximum levels of higher alcohols in alcoholic beverages, data on the toxicity of higher alcohols were obtained by a computer-assisted literature search in the following databases: PubMed, Toxnet and ChemIDplus (U.S. National Library of Medicine, Bethesda, MD), Web of Science (Thomson Scientific, Philadelphia, PA), IPCS/INCHEM (International Programme on Chemical Safety/Chemical Safety Information from Intergovernmental Organizations, WHO, Geneva, Switzerland), Food Science and Technology Abstracts (International Food Information Service, Sharnfield, UK), and Scopus (Elsevier B.V., Amsterdam, Netherlands). The references, including abstracts, were imported into Reference Manager V.11 (Thomson ISI Research Soft, Carlsbad, CA) and the relevant articles were manually identified and purchased in full text. The reference lists of all articles were checked for relevant studies not included in the databases.

## 3. Results and discussion

### 3.1. Acute toxicity of higher alcohols

As early as 1869, Richardson pointed out that the potency of aliphatic alcohols increases with their molecular

weight (Richardson, 1869). This has come to be known as Richardson’s law. The law was verified by numerous studies (e.g., Lehman and Newman, 1937; MacGregor et al., 1964; McLaughlin et al., 1964; Munch and Schwartz, 1925; Weese, 1928; Welch and Slocum, 1943). In 1907, Fühner and Neubauer (1907) concluded the toxicity as measured by narcotic and haemolytic activity of normal monohydric alcohols from ethyl to octyl to be in the relation of  $1:3^1:3^2:3^3:3^4:3^5$ . This received confirmation in the work of Kamm (1921), who found that it held approximately true when the toxicity of these alcohols to paramecia was determined.

A third generalization was made by Macht (1920) when it was found that the *iso*-alcohols were less toxic to cats than the corresponding normal isomer. Beer and Quastel (1958) and Wallgren (1960) confirmed that toxicity and narcotic effects of aliphatic alcohols seem to increase with increasing length of the carbon chain and decrease from primary to secondary and from secondary to tertiary alcohols.

In the context of Richardson’s law one restriction must be mentioned. As early as 1920, Macht (1920) had pointed out a possible error in interpreting the available data collected in studies on acute toxicity, and called attention to the possibility of more toxic metabolites. Murphree et al. (1967) pointed out some obvious problems: Richardson’s law applies only to primary toxic effects. For example, methanol is of course more toxic than ethanol because of its metabolites, formaldehyde and formic acid. Skog (1950) noted that for aldehydes, the toxicity decreased with an increase of molecular weight, and this applied whether the aldehyde was saturated or unsaturated. Richardson’s law obviously does not apply to the aldehydes. Thus while it is true that methanol is less toxic than ethanol acutely, this does not take into account the optic nerve damage caused by methanol, which appears only after a latent period.

The acute toxicity of alcohols was summarized by the International Programme on Chemical Safety (IPCS, 1987a, 1990, 1997), as well as the OECD SIDS programme (OECD SIDS, 2004). Data about the acute oral toxicity of alcohols and their metabolites in rats are summarized in Table 1.

### 3.2. Chronic toxicity, liver toxicity and neurotoxic effects of higher alcohols

Long-chain aliphatic alcohols contained in products not intentionally produced for consumption (e.g., antifreeze) but also in home-made products intended as beverage alcohol have been linked with a higher hepatotoxicity. However, the occurrence and severity of detrimental health outcomes clearly depends on the concentration of these substances. So far it is unclear if the relatively low content of higher alcohols in combination with high concentrations of ethanol have a consequence on the etiology of liver diseases. Gibel et al. (1969) reported severe hepatic damage

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