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Ethyl carbamate in alcoholic beverages from China: Levels, dietary intake, and risk assessment

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ABSTRACT

A national survey of ethyl carbamate (EC) in alcoholic beverages from the fourth and fifth Chinese total diet study (TDS) performed in 2007 and 2009 was conducted for the first time. Alcoholic beverages samples were collected from 16 provinces representing the average dietary patterns of various provinces of China and covering about 60% of the total Chinese population. The results showed that the average EC level in alcoholic beverages (19.8 μg/kg) in the fifth TDS was higher than that of the fourth TDS (8.5 μg/kg). The dietary intake of EC from the Chinese population was estimated to be 8.27 ng/kg bw per day for average population and 45.67 ng/kg bw per day for high consumers (the 97.5th percentile) in the fifth TDS. The average and high-end estimated daily intakes of EC for the alcoholic beverages were both lower than estimated daily intake (EDI) value (80 ng/kg bw per day) suggested by JECFA, indicating low health risk of EC dietary exposure among Chinese adults at present.

The Chinese rice wines, as a kind of traditional fermented alcoholic beverages in China, has a high level of EC and an obvious consumption regional disparity, thus the health risk of EC in Chinese rice wines should be of concern. To estimate the daily intake of EC from Chinese rice wines consumed in China, 890 Chinese rice wines samples including 468 commercial wines and 422 base wines were collected from various regions. The distribution of EC varied significantly among 468 commercial wines, ranging from 6.3 to 775.8 μg/L (mean: 232.9 μg/L). Based on the intake data for Chinese rice wines from the food consumption survey, the daily intake of EC was estimated to be 290.6 ng/kg bw per day for average consumers and 1848.4 ng/kg bw per day for high consumers (the 97.5th percentile). In this study, the estimated daily intake of EC for Chinese rice wines in China was far higher than EDI value suggested by JECFA indicating that Chinese rice wines were the main exposure origin of EC in alcoholic beverages. Health risk assessment of EC using a margin of exposure (MOE) approach recommended by the European Food Safety Authority (EFSA) suggested unlikely health concern with respect to current dietary intake of EC for alcoholic beverages in China. However, a relatively high health risk of EC dietary exposure in Chinese rice wines was observed in some provinces. Therefore, some adapted strategies should be developed and used in industrial scale to control the level of EC for Chinese rice wines.

1. Introduction

Ethyl carbamate (EC), known as urethane, is a multi-site genotoxic carcinogen in animals and classified as a group 2A carcinogen (probably carcinogenic to humans) by the World Health Organization's International Agency for Research on Cancer (IARC) (IARC, 2010). This toxicant occurs naturally in alcoholic beverages and most fermented foods (Dennis, Howarth, Key, & Mases, 1989; Kim, Koh, Chung, & Kown, 2000; Riachi, Santos, Moreira, & De Maria, 2014; Weber & Sharypov, 2009). Previous studies have indicated that EC in alcoholic beverages primarily results from the reaction of ethanol and nitrogen-containing compounds, such as urea, carbamyl phosphate and cyanide (Hasnip, Caputi, Crews, & Brereton, 2004; Li et al., 2015; Wu et al., 2014; Zhao et al., 2013). These main EC precursors are commonly generated from arginine metabolism by *Saccharomyces cerevisiae* or lactic acid bacteria accompanied by the fermentation process (Nobrega et al., 2015). The

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presence of EC in alcoholic beverages first drew attention when a relatively high level of EC was detected in imported fermented alcoholic beverages (Conacher & Page, 1986). Due to its carcinogenicity and high levels in fermented beverages, many countries have started to set control measures to effectively regulate the amount of EC in food products. Although there is currently no uniform maximum level established for EC in the European Union (EU), worldwide many countries have established their own criteria. For example, the Canadian Government set a maximum level for EC in different types of alcoholic beverages, ranging from 30 μg/L (wine) to 400 μg/L (fruit brandies) (Hong et al., 2007). The Czech Republic had a regulation similar to that of Canada (Weber & Sharypov, 2009). Moreover, the maximum levels of EC were set as 150 μg/L and 1000 μg/L for distilled spirits and fruit brandies respectively in France, and 800 μg/L for fruit brandies in Germany (Weber & Sharypov, 2009). In Korea, a regulation on maximum allowable levels of EC had only been applied to grape wine (i.e., <30 μg/kg) (Lim & Lee, 2011).

As estimated by the JECFA (Joint FAO/WHO Food Standards Programme 2007, JECFA), the Benchmark Dose Lower Limit ($BMDL_{10}$) of EC for the lung tumors as the critical end-point in mice is 0.3 mg/kg bw per day and the mean intake of EC from food excluding alcohol beverages to be approximately 15 ng/kg bw per day. With the inclusion of alcoholic beverages the estimated intake is 80 ng/kg bw per day. The European Food Safety Authority (EFSA) recently indicated that whenever genotoxic and carcinogenic compounds are present in a botanical or botanical preparation of interest, the margin of exposure (MOE) approach (EFSA., 2005) can be used to evaluate the potential risk for human health and the priority for risk management actions. The MOE of EC, defined as the ratio of $BMDL_{10}$ to the estimated dietary intake of EC in humans, was then calculated and used by the Committee as an index for the assessment of the potential health risk posed by EC to humans. With the inclusion of alcoholic beverages in the estimated intake (80 ng/kg bw per day), the resulting MOE is 3800. According to EFSA. (2005), the Scientific Committee is of the view that in general an MOE of 10,000 or higher would be of low concern from a public health point of view and might be considered as a low priority for risk management actions. On the basis of these considerations, the Committee concluded that the intake of EC from foods excluding alcoholic beverages would be of low concern (JECFA, 2005, 2006). However, the MOE for all intakes, food and alcoholic beverages combined, is of concern and some measures to reduce concentrations of EC in some alcoholic beverages should be continued.

Previous studies for the levels of EC in fermented foods and alcoholic beverages and risk assessments mainly focused on the food items of the Western diet. Little was known about the amount of EC in fermented foods and alcoholic beverages of the Eastern diet which are commonly consumed by a large number of population worldwide (Lee, 2013; Tang et al., 2011). In China, large numbers of alcoholic beverages are produced and consumed every year. For example, in 2009, about 7.06 million tons of white spirits and 0.96 million tons of wines were made in China. However, for alcoholic beverages from Zhejiang, China, the concentrations of EC ranged from 2 to 515 μg/kg with an average level of 160 μg/kg in Chinese rice wine, 87 μg/kg in rice cooking wine, 72 μg/kg in white spirits, 16 μg/kg in wine, and 2 μg/kg in beer (Wu, Pan, Wang, Shen, & Yang, 2012). Alcoholic beverages are an important source of EC owing to their high daily consumption in China. In addition, the Chinese rice wines, as a kind of traditional fermented alcoholic beverages in China, has a high level of EC and an obvious consumption regional disparity (Fu et al., 2010; Wang, Wu, Zhou, & Chen, 2014). Therefore, the daily EC intake from alcoholic beverages in the Chinese population needs to be investigated more thoroughly prior to taking actions to reduce EC levels.

The aim of this study was to assess the general population's dietary exposure to EC from alcoholic beverages by the Chinese total diet study (TDS) approach in 2007 and 2009. In addition, an EC analysis in 890 Chinese rice wines samples including 468 commercial wines and 422 base wines were conducted to estimate the daily intake of EC from Chinese rice wines consumed in some provinces from China.

2. Materials and method

2.1. Reagents and materials

All solvents (n-hexane, diethyl ether, ethyl acetate, methanol) were used of gas chromatography (GC) grade, and all reagents of analytical grade (anhydrous sodium sulfate and NaCl) were used. The diatomaceous earth cartridge was Extrelut NT20 columns (20-mL) (Merck, Darmstadt, Germany). EC and d_5-EC were purchased from Sigma–Aldrich (St. Louis, MO, USA) and the purity was above 99%.

2.2. Food consumption survey and sampling

2.2.1. Alcoholic beverages consumption survey and sampling for Chinese TDS

The food consumption survey for TDS was organized by the Chinese Center for Disease Control and Prevention in 2007 and 2009. Details on sampling methodology of the TDS in China were published elsewhere (Li, Wu, Zhang, & Zhao, 2007; Zhang et al., 2013; Zhou et al., 2012). First, all provinces from China were classified into four geographical regions according to geographical attribute and resident dietary pattern. Then, 4 provinces were randomly sampled from each region. The 16 provinces were Heilongjiang, Liaoning, Hebei, Shanxi, Ningxia, Henan, Shanghai, Fujian, Jiangxi, Guangxi, Hubei, Sichuan, Beijing, Jiangsu, Zhejiang and Hunan covering about 60% of the total Chinese population. In each province, three sampling sites including one urban site and two rural sites were randomly selected, and then 30 households were randomly sampled from each site to conduct the food consumption survey by a 3-day household dietary survey that documented all of the food consumption by a weighing and recording method. All food items were aggregated into 12 groups including alcoholic beverages, and then the average food consumption was calculated to present the pattern of food consumption. According to the pattern of food consumption, food samples were collected from local food markets, grocery stores, or rural households in each sampling site and then prepared using local practice and recipes. The composite of mixed alcoholic beverages was made by blending the prepared individual alcoholic beverage with weights proportional to the average daily consumption in each province. These provincial composites were shipped to the China National Center for Food Safety Risk Assessment and frozen at −20 °C until analysis.

2.2.2. Consumption data and sampling for Chinese rice wines

The samples of Chinese rice wines were collected from manufacturing enterprises in Zhejiang, Jiangsu, Shandong, Fujian, Shanghai, Anhui and Hunan provinces, which included 468 commercial wines and 422 base wines. The questionnaires survey were mainly distributed in Chinese rice wines consumption provinces (Zhejiang, Jiangsu, Shandong, Anhui and Hunan provinces). In each province, the survey sites were selected based on the local Chinese rice wines consumption pattern. The consumption pattern was determined by a 3-day household dietary survey and 24-h recalls for those of 18–55 years of age. Finally, the survey covers 3284 individuals in total, 2513 questionnaires of which was valid and useful. The mean quantities of Chinese rice wines consumed per