NO SIGNIFICANT RISK LEVELS (NSRLs) FOR THE PROPOSITION 65 CARCINOGEN ETHYLBENZENE

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SUMMARY OF FINDINGS

Inhalation and oral human cancer potencies for ethylbenzene were developed based on an analysis by the Office of Environmental Health Hazard Assessment (OEHHA) under the Air Toxics Hot Spots and Toxic Air Contaminant (TAC) programs. The linearized multistage model was applied to dose-response data for renal tubule adenomas or carcinomas (combined) in male F344 rats exposed to ethylbenzene via inhalation (NTP, 1999; OEHHA, 2007) to derive the inhalation cancer potency. The potency derivation takes into account body size differences between humans and experimental animals. The oral human cancer potency was derived from the inhalation human cancer potency based on the ratio of the uptake factors for the inhalation versus the oral routes. The Proposition 65 "no significant risk level" (NSRL) is defined in regulation as the daily intake level posing a 10^{-5} lifetime risk of cancer. The inhalation and oral human cancer potency estimates for ethylbenzene are shown in Table 1, along with the corresponding NSRLs.

Table 1. Cancer Potencies and NSRLs for Ethylbenzene.

Exposure Route	Human Cancer Potency $(mg/kg\text{-}day)^{-1}$	NSRL (μg/day)
Inhalation	0.013	54
Oral	0.017	41

INTRODUCTION

Ethylbenzene (CAS number 100-41-4) was listed on June 11, 2004 as a chemical known to the State to cause cancer under Proposition 65 (formally known as the Safe Drinking Water and Toxic Enforcement Act of 1986; California Health and Safety Code 25249.5 *et seq*.). Ethylbenzene is found in gasoline and diesel fuel and is also used as a chemical intermediate. The volume produced in or imported into the U.S. was reported to be >1 billion pounds in 2002 (U.S. Environmental Protection Agency, 2002).

OEHHA (2007) developed a unit risk factor and oral and inhalation human cancer potencies for ethylbenzene under the Air Hot Spots and Toxic Air Contaminant Programs. These values were generated assuming an interspecies conversion factor from animal potency to human potency

based on the ratio of human to animal body weights raised to the one-quarter power. The Proposition 65 regulations (Title 22, California Code of Regulations, section 12703) specify that the interspecies conversion of the animal potency to the human potency should be the ratio of human and animal body weights taken to the one-third power. The animal cancer potency estimate reported in the OEHHA (2007) analysis of ethylbenzene was therefore converted to a human cancer potency estimate using the interspecies conversion factor specified in the Proposition 65 regulations, as described in more detail below.

DERIVATION OF HUMAN CANCER POTENCY

OEHHA (2007) derived an inhalation animal cancer potency of 0.002472 $(mg/kg\text{-}day)^{-1}$ for ethylbenzene. The animal cancer potency was estimated from the National Toxicology Program (NTP, 1999) bioassay results of renal tubule carcinomas or adenomas (combined) in male rats exposed to ethylbenzene via inhalation using a linearized multistage analysis (OEHHA, 2007).

As specified in Title 22, California Code of Regulations, section 12703(a)(6), an interspecies conversion factor is applied to the animal cancer potency (q_{animal}) to determine the human cancer potency (q_{human}) under Proposition 65 as follows:

$$q_{human} = q_{animal} \times \left(\frac{bw_h}{bw_a} \right)^{\frac{1}{3}} \quad (1)$$

The body weights for humans (bw_h) and male rats (bw_a) are 70 kg and 0.450 kg, respectively. The inhalation animal cancer potency (q_{animal}) is 0.002472 $(mg/kg\text{-}day)^{-1}$ (OEHHA, 2007). Thus, the inhalation human cancer potency estimate (q_{human}) under Proposition 65 would be:

$$q_{human} = 0.002472\,(mg/kg-day)^{-1} \times \left(\frac{70}{0.450} \right)^{\frac{1}{3}} = 0.013\,(mg/kg\text{-}day)^{-1}$$

Based on OEHHA (2007), the uptake of ethylbenzene via inhalation is assumed to be 77% (or 0.77), while the oral uptake is 100% (or 1). To determine the oral cancer potency, the inhalation cancer potency is multiplied by the ratio of oral to inhalation uptake factors, as follows:

$$q_{human\_oral} = q_{human\_inh} \times \frac{uptake_{oral}}{uptake_{inh}} = 0.013\,(mg/kg\text{-}day)^{-1} \times \frac{1}{0.77} = 0.017\,(mg/kg\text{-}day)^{-1}$$

Therefore, the oral human cancer potency estimate of 0.017 $(mg/kg\text{-}day)^{-1}$ is derived from the inhalation human cancer potency estimate of 0.013 $(mg/kg\text{-}day)^{-1}$.

ESTIMATION OF NSRL

The no significant risk level (NSRL) in units (mg/day) for a 70 kg person is calculated according to the following equation:

$$NSRL = \frac{10^{-5} \times 70\,kg}{q_{human}} \quad (2)$$

where q_{human} is the human cancer potency in units $(mg/kg\text{-}day)^{-1}$.

The calculations for the inhalation and oral NSRLs in units (µg/day) are shown below:

$$NSRL_{inhalation} = \frac{10^{-5} \times 70\,kg}{0.013\,(mg/kg\text{-}day)^{-1}} \times 1000\,\mu g/mg = 54\,\mu g/day$$

$$NSRL_{oral} = \frac{10^{-5} \times 70\,kg}{0.017\,(mg/kg\text{-}day)^{-1}} \times 1000\,\mu g/mg = 41\,\mu g/day$$

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