Ethylene oxide in ethylene-exposed mice, rats, and humans

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Abstract

The olefin ethylene (ET) is a ubiquitously found gas. It originates predominantly from industrial sources but also from plants in which it acts as a ripening hormone. In mammals, it is metabolized to ethylene oxide (EO), a protein and DNA alkylating epoxide that was mutagenic in vitro and in vivo and carcinogenic in rats and mice. In order to predict the EO burden of EO- and ET-exposed rodents and humans, a physiological toxicokinetic (PT) model had been developed (Csanády et al., 2000). Although predicted concentration-time courses of ET or EO resulting from exposures to ET or EO, respectively, were in agreement with measured data, EO could not be predicted well when it was metabolically formed from ET. In order to solve this problem,

- we investigated the kinetics of the formation of EO from ET and of its elimination in liver cell fractions of male B6C3F1 mice, male F344 rats, and humans of both genders;
- we measured EO in blood of ET-exposed male B6C3F1 mice, male F344 rats, and male humans.

The results of both studies have meanwhile been published (Lee et al., 2011 and Filser et al., 2013). In liver microsomes of the three species, ET metabolism to EO was rapidly inhibited by ET-induced suicide inactivation of CYP2E1. Metabolism of EO by microsomal epoxide hydrolase could be quantified only in microsomes of humans. In those of mice and rats, it was below the limit of detection. In liver cytosol of the three species, EO was effectively eliminated by glutathione S-transferase-mediated conjugation of EO with glutathione. In vivo, EO was quantified in venous blood of ET-exposed mice, rats, and humans at ET concentrations in air ranging from 1 to 10000 ppm (animals) and from 5 to 50 ppm (humans). Up to ET concentrations of about 100 ppm (animals) and 50 ppm (humans), EO concentrations in blood increased to plateaus that were reached 2 – 3 hours after starting the exposures. At 300 ppm of ET and above, EO in animal blood peaked shortly after starting the exposures. Thereafter, it decreased to species-specific plateau levels that were similar regardless whether the exposure concentration of ET was 300 or 10000 ppm.
Hitherto, a PT model has been developed for inhaled ET or EO in F344 rats which is based on the available in vitro and in vivo data. Incorporated is the ET-mediated suicide inhibition of the ET metabolizing CYP2E1 together with its physiological turnover. The model predicted in agreement with measured data not only concentration-time courses of ET or EO resulting from exposures to ET or EO, respectively, but also those of metabolically formed EO resulting from various exposures to ET. In addition, model-predicted destruction of CYP2E1 by ET agrees with measured data. After extending the model for mice and humans, it will be a powerful tool for risk assessment of ET or EO.