Uptake of Inspired Propylene Oxide in the Upper Respiratory Tract of the F344 Rat

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Propylene oxide (1,2-epoxypropane, CAS# 75-56-9) is a nasal toxicant and weak site-of-contact carcinogen in the rodent. The current study was aimed at providing quantitative information on upper respiratory tract (URT) dosimetry of this vapor. Since depletion of nasal non-protein sulfhydryls (NPSH) may be important in the toxicity of this vapor and may serve as a biomarker for delivery of propylene oxide to nasal tissues, measurements of respiratory and olfactory NPSH content after propylene oxide exposure were also made. Towards these ends, uptake of this vapor was measured in the surgically isolated URT of the F344 rat at constant velocity inspiratory flow rates of 50 or 200 ml/min throughout a 60-min exposure. Immediately after exposure, nasal respiratory and olfactory tissues were removed and analyzed for NPSH content. Propylene oxide was scrubbed from the airstream with moderate efficiency in the isolated URT. Similar uptake efficiencies were observed at inspired concentrations of 25, 50, 100, and 300 ppm, averaging 25 and 11% at flow rates of 50 and 200 ml/min, respectively. After 1-h exposure to concentrations of 100 ppm or more, statistically significant depletion of nasal respiratory mucosal NPSH was observed. Nasal respiratory mucosal NPSH levels averaged approximately 90, 70, 50, 40, and 15% of control levels after 1-h exposure to 25, 50, 100, 300, or 500 ppm propylene oxide. Olfactory mucosal NPSH levels also generally decreased at 300 or 500 ppm propylene oxide, but did not demonstrate statistically significant, consistent changes after propylene oxide exposure.

Key Words: propylene oxide; upper respiratory tract; F344 rat; nasal non-protein sulfhydryls.

Propylene oxide metabolism and kinetics have been studied in microsomes and cytosol by Faller et al. (2001). This compound can hydrolyze spontaneously at a very slow rate (k = 0.04 h⁻¹) or can react directly with glutathione (GSH, k = 0.4 h⁻¹ at GSH = 15 mM). It can be metabolized via conjugation with GSH, mediated by cytosolic glutathione-S-transferase (GST), or hydrolyzed to propylene glycol by microsomal epoxide hydrolase (EH). In vitro metabolic constants for these pathways have been determined for both respiratory and olfactory nasal mucosa of the rat (Faller et al., 2001). In respiratory mucosa the Vmax for the GST-mediated conjugation is ~70 nmol/min/mg cytosolic protein; the Vmax for epoxide hydrolase hydrolysis is ~40 nmol/min/mg microsomal protein. Since cellular protein content in the microsomal fraction is typically much lower than cytosolic fraction, these results suggest the GST pathway may be a quantitatively more significant pathway in rodent nasal tissues in terms of total propylene oxide clearance. Recent studies have shown that propylene oxide inhalation results in depletion of nasal non-protein sulphydryl (NPSH) content (Lee et al., 1998, 1999, 2000).
Quantitative dose-response assessment for propylene oxide would be aided by knowledge of nasal dosimetry and development of an appropriate dosimetry model for this vapor. The aim of the current study was to provide quantitative data on uptake of propylene oxide by rodent upper respiratory tract (URT, defined as all regions of the respiratory tract anterior to and including the larynx), with the long-term goal of facilitating the development of such a model. Towards this end, uptake of propylene oxide was measured under constant velocity inspiratory flow conditions in the surgically isolated URT of the F344 rat by standard techniques (Morris, 1999) over a range of exposure times and concentrations. Since models make specific predictions on the effect of inspiratory flow rate on uptake efficiencies, uptake was measured at two inspiratory flow rates. Because depletion of nasal NPSH provides a biomarker of delivery of propylene oxide to nasal tissues, and since it may be mechanistically important in the toxicity of this compound, the current studies also included measurement of nasal NPSH levels in both the respiratory and olfactory tissues.

The initial studies were focused on obtaining time and concentration range-finding data on NPSH depletion by propylene oxide to facilitate the optimization of the exposure protocol for the subsequent uptake studies. A time-course study was performed first in which rats were exposed to 300 ppm for 15, 30, 45, and 60 min. (This concentration was selected as one that was likely to result in significant NPSH depletion; Lee et al., 1998, 2000.) The time-course study was followed by a range-finding concentration-response study in which rats were exposed to 50, 100, 300, or 500 ppm propylene oxide for 60 min. In both the time-course and range-finding studies, a single inspiratory flow rate (200 ml/min) was used. Based on the results of these studies, the subsequent URT uptake study was performed at exposure concentrations of 25, 50, 100, or 300 ppm. Two flow rates, 50 or 200 ml/min, were used in this study.

MATERIALS AND METHODS

Animals, surgical procedure, and tissue collection. Male F344 rats (Charles River, Wilmington, MA, VAF/Plus Crl:CDBR, 125–150 g at time of purchase) were used in all experiments. Animals were housed over hard wood bedding in animal rooms maintained at 22–25°C with a 12 h light-dark cycle (lights on at 0630 h). Food (Lab Diet, PMI Nutrition International, Brentwood, MO) and tap water were provided (lights on at 0630 h). Food (Lab Diet, PMI Nutrition International, Brentwood, NJ) was inserted in an anterior direction until its tip was at the larynx, and then was tied in place. Exposures of the surgically prepared rats were performed as described below.

Immediately after exposure, each animal was killed by exsanguination via incision of the abdominal vena cava. The vasculature was then perfused with 30 ml saline to remove residual blood. The skull was removed and split sagitally and tissues from the nasal cavity were removed to prepare two homogenates as described by Casanova-Schmitz et al. (1984). The respiratory mucosa homogenate contained tissue from the nasomaxillary turbinate and adjacent septal mucosa; the olfactory mucosa homogenate contained the yellow-tinted olfactory mucosa lining the dorsomedial meatus and the tissues from the ethmoturbinate and adjacent septal mucosa. The respiratory and olfactory mucosa homogenates contained ~3 and ~6 mg protein, respectively (method of Lowry et al., 1951).

The entire collection procedure was completed within 5–10 min after terminal sacrifice. Tissues were homogenized in ice cold 5% trichloroacetic acid with 3 mM EDTA and spun at 10,000 × g for 5 min. The resulting supernatant was stored on ice for subsequent non-protein sulphydryl (NPSH) analysis.

Exposure condition. Rats were exposed in a 0.5-l PVC nose-only exposure chamber. Chamber air flow rates were maintained at 5–10 l/min (depending on the exposure concentration) with clean, heated, and humidified air. Chamber air temperature averaged approximately 40°C, water content approximately 33 mg/l, corresponding to greater than 75% relative humidity at 37°C. The chamber walls and air supply lines were heated to prevent condensation.

Propylene oxide atmospheres were generated by feeding the liquid via a syringe pump into a glass T tube maintained at approximately 60°C through which 0.8 l/min of air was passed. The vapor-rich air was then passed through a mixing chamber and into the nose-only exposure chamber. Propylene oxide (reagent grade, ≥98%) was obtained from Fisher Scientific (Pittsburgh, PA). The exposure chamber and vapor generation apparatus were housed in a fume hood.

Uptake measurement. The precise methodology for exposure and measurement of URT uptake efficiency has been described in detail (Morris, 1999). Briefly, the surgically prepared animal was placed in the nose-only chamber in a supine position and the endotracheal tube was connected to an air sample train. This sampling system served to draw the chamber air through the isolated URT under constant velocity flow conditions at flows of 50 or 200 ml/min. These flows are within the physiological range for the rat of about 150 ml/min (Morris, 1999). During exposure the animal respired room air through the incised trachea.

The sample train contained a 15 ml glass trap with three ports. The trap was connected to the exposure chamber or the endotracheal tube of the surgically prepared animal with polyethylene tubing. Air was drawn off the trap at a flow rate of 7 ml/min for analysis (see below) via the second port. Total flow rates were maintained at 50 or 200 ml/min by drawing air from the third port at the necessary flow rate. Air flow rates were controlled by rotameters that were calibrated in the sample line with a bubble meter.

Measurement of uptake efficiency requires determination of the propylene oxide concentration in air entering the URT (Cin) as well as the concentration in air exiting the URT (Cex). Uptake efficiency is calculated from the ratio of the concentrations in these samples as described previously (Morris, 1999). To determine Cin, the sample train was connected directly to the chamber both immediately before and immediately after the animal exposure. The ratio of the before and after Cin concentrations averaged 100.4 ± 6.0% (mean ± SD) indicating the chamber concentration remained constant. For measurement of Cex, the sample train was connected to the endotracheal tube. Air samples were injected into a gas chromatograph at 3-min intervals (see below) to provide a continuous measurement of Cex concentration throughout the exposure.

Analytical procedures. Airborne propylene oxide levels were determined by gas chromatography (Varian model 3600 gas chromatograph, FID detection). Towards this end, air was drawn off the trap in the sample train (see above) at a flow rate of 7 ml/min through an eight-port gas sampling valve equipped with two 0.5 ml sampling loops. The valve injected the 0.5 ml sample onto the column (15 meter DB-WAX megabore, J&W Scientific) at 3-min intervals. The column temperature was maintained at 33°C. The carrier gas (nitrogen) flow rate was 30 ml/min. Under these conditions an entire chromatogram could be completed in 2.5 min. Propylene oxide retention time was 0.2 min. Peak areas were converted
to airborne concentration on the basis of standard curves generated by injecting pure propylene oxide (using a cold gas tight syringe) into 4.3-l glass bottles, allowing 5–10 min for equilibration, and drawing air from the bottle at 7 ml/min through the gas sample valve. Standard curves were run throughout the study (at approximately two-week intervals), the slopes of which agreed within 10%. A single composite standard curve comprised of all the standard curves prepared during the study (for which $r^2 > 0.97$) was used to calculate all airborne concentrations.

Tissue homogenate supernatants were analyzed spectrophotometrically for NPSH content by the method of Sedlack and Lindsay (1968) using glutathione (Sigma Aldrich, St. Louis, MO) as a standard. Data are presented as total NPSH content by the method of Sedlack and Lindsay (1968) using glutathione concentrations.

Statistics. Data are reported as mean ± SEM unless otherwise indicated. Each group contained 6–8 animals, unless otherwise stated. NPSH data were log transformed due to heteroscedasticity. Data were compared by ANOVA followed by Newman-Keuls test. A $p < 0.05$ was required for significance.

RESULTS

Time-Course

Groups of six rats each were exposed to 300 ppm propylene oxide for 15, 30, 45, or 60 min at a flow rate of 200 ml/min. Measured propylene oxide concentration averaged 313 ± 17 ppm (mean ± SD). For controls, groups of three rats each were exposed to clean air for 15, 30, 45, or 60 min. ANOVA revealed no significant difference in respiratory or in olfactory tissue NPSH content across these time points in the control animals indicating that tissue NPSH levels remain stable during the URT exposure procedure. The control data for all time points were combined to form single, respiratory or olfactory tissue control groups for subsequent statistical analysis.

Shown in Figure 1 are the respiratory and olfactory mucosal NPSH levels in the time-course experiment. Control data represents the combined control values (see above); total NPSH content in the respiratory and olfactory mucosal samples averaged 89 and 327 nmol (corresponding to ~30 and ~55 nmol/mg protein), respectively. Separate statistical analyses were performed on the respiratory and the olfactory tissue. Exposure to propylene oxide resulted in significant depletion of respiratory mucosal NPSH ($p = 0.0001$, ANOVA). NPSH levels after 30 min of exposure were approximately one-half of control levels ($p < 0.05$ compared to control, Newman-Keuls test). Although not statistically different from the values at 30 or 45 min, after 60 min of exposure there appeared to be a greater degree of depletion with levels averaging approximately one-quarter of control values ($p < 0.05$ compare to control). Significant differences were observed in olfactory mucosal NPSH level among the exposure groups ($p = 0.002$, ANOVA). Newman-Keuls test revealed that only in the 60-min group were NPSH levels statistically significantly ($p < 0.05$) lower than control levels. NPSH levels at this time point were approximately one-third of control levels.

Concentration-Response Range-Finding Study

Based on the results of the time-course study, the concentration-response study was performed using 60-min exposures to allow the maximal practicable time for NPSH depletion to occur, particularly in olfactory tissue. Groups of six animals each were exposed to 50, 100, 300, or 500 ppm propylene oxide. Exposure concentrations averaged (mean ± SD) 42 ± 11, 103 ± 8, 309 ± 36, and 487 ± 32 ppm propylene oxide in these groups, respectively. Results of the concentration-response study are shown in Figure 2. Control levels in this experiment were similar to those observed in the time-course experiment (Fig. 1), averaging 76 and 332 nmol NPSH in respiratory and olfactory mucosa, respectively (corresponding to ~25 and ~55 nmol/mg protein). Separate statistical analyses were performed for data from the respiratory and olfactory samples.

Respiratory mucosal NPSH levels differed significantly among the exposure groups ($p = 0.0001$, ANOVA). Following a 60-min exposure to propylene oxide, respiratory mucosal NPSH levels were approximately 70, 45, 35, and 15% of control levels in animals exposed to 50, 100, 300, or 500 ppm, respectively. Levels in all exposure groups were significantly less than control, with the levels in the 500 ppm group being the lowest ($p < 0.05$, Newman-Keuls test). The degree of NPSH depletion observed in the 300 ppm group this study was similar to that observed at 60 min in the time-course study (see Fig. 1).

Olfactory mucosal NPSH levels differed significantly among the exposure groups ($p = 0.03$, ANOVA). Although the mean values for NPSH from all tested groups of PO-exposed rats were lower than control values, Newman-Keuls test revealed that only values from the 300 ppm group were statistically significantly lower than control levels. No other statistically significant differences were observed. Thus, a clear concentration-response relationship was not observed, perhaps due to the variability in the data. Considerable variability in olfactory mucosal NPSH levels has been reported previously (Frederick et al., 2002). Interestingly, among the 500 ppm group animals, two rats displayed no NPSH depletion (levels greater than control), whereas the remaining five animals demonstrated marked depletion (levels less than 50% of control; mean values of 37 ± 9% of control values). The reasons for this wide variability in olfactory mucosal NPSH response are unknown. Respiratory mucosal NPSH levels were similarly depleted in all the rats, including the two non-responding animals. Perhaps there were differences in the fraction of inspired air that passed over the olfactory epithelium in the two rats that did not demonstrate any NPSH depletion in olfactory mucosal tissue.

Uptake Efficiency Study

Groups of eight rats each were exposed to 0, 25, 50, 100, or 300 ppm propylene oxide for 60 min, at a flow rate of either 50 or 200 ml/min. Measured propylene oxide concentrations averaged 28 ± 1, 47 ± 3, 102 ± 4, or 308 ± 9 ppm (mean ± SD). A 60-min exposure period was selected to provide the
maximal practicable time for NPSH depletion. The 25 ppm exposure group was included to determine if depletion of NPSH could be observed at this exposure concentration (statistically significant depletion of NPSH was observed at 50 ppm in the range-finding study, see above).

Shown in Figure 3 is propylene oxide uptake efficiency during exposure to 300 ppm at both 50 and 200 ml/min flow rate. As can be seen, uptake efficiency remained steady during the 60-min exposure. Uptake data were analyzed by two factor repeated measures ANOVA with the factors being flow rate (50 or 200 ml/min), and exposure concentration (25, 50, 100, or 300 ppm), and the repeated measure being exposure time. This analysis revealed a significant effect of flow rate ($p < 0.0005$). Uptake efficiency was statistically similar at all concentrations ($p > 0.05$) and at all exposure times ($p > 0.05$), the latter result confirming that steady state conditions were apparently maintained. No statistical interactions were detected. Shown in Table 1 are the average uptake efficiencies in each exposure group. As in our previous studies (Morris, 1999), uptake efficiencies during the last one-half of exposure were averaged to provide these data; similar results would be obtained if the average over the entire exposure period were used. Uptake
averaged approximately 25% efficient at the 50 ml/min flow rate compared to approximately 11% efficient at the 200 ml/min flow rate, regardless of the exposure concentration. The total delivered dose rate for propylene oxide can be calculated as the product of the inspired concentration, inspiratory flow rate, and uptake efficiency. Such calculation results in the following delivered dose rates for 25, 50, 100, and 300 ppm propylene oxide at flow rates of 50 and 200 ml/min, respectively: 10, 20, 50, and 130 nmol/min (50 ml/min flow rate) and 25, 45, 90, and 290 nmol/min (flow rate of 200 ml/min).

Shown in Figure 4 are the respiratory and olfactory mucosal NPSH content results for the animals of the uptake study. Data from each tissue were compared separately. Control tissue NPSH levels were similar to those observed previously, averaging 74 and 257 nmol in respiratory and olfactory mucosa, respectively (corresponding to ~25 nmol/mg protein). Groups with differing superscripts (a,b,c) differ significantly ($p < 0.05$, ANOVA followed by Newman-Keuls test). See text for details.
concentration detected \((p > 0.05)\). Newman-Keuls test revealed NPSH was statistically significantly lower than control levels \((p < 0.05)\) in respiratory mucosa from the 100 and 300 ppm groups, but not the 25 or 50 ppm groups, although the mean values for the PO-exposed animals were lower. The slope of the concentration response relationship appears relatively shallow. For example a doubling of the exposure concentration (e.g., 50 to 100 ppm) results in only a relatively small change in NPSH content (from \(~80\) to \(~65\%\), respectively, \(p > 0.05\)). Olfactory mucosal NPSH levels appeared similar to controls at all exposure concentrations. For this tissue the two-factor ANOVA did not detect a significant effect of flow rate, nor any effect of exposure concentration, nor any interaction between the two factors \((p > 0.05)\). Although this result differs from that observed previously (Fig. 2b), comparison of these two experiments by multifactorial ANOVA failed to detect a significant difference between them \((p = 0.54)\), perhaps due to the variability in the olfactory data, in particular from the uptake experiment.

**DISCUSSION**

Moderate uptake efficiencies (25% or less) were observed for propylene oxide in the current study. URT vapor uptake processes are well understood from a theoretical perspective. Under constant velocity flow conditions, steady state uptake of vapors is dependent upon the rate at which vapor molecules can be removed from nasal tissues either via the circulation, via metabolism and/or via direct reaction with nasal tissue substrates (Medinsky et al., 1999; Morris, 1994). Since propylene oxide can react directly with glutathione, can be metabolized via glutathione S-transferase (GST) or epoxide hydrolase (EH) (Faller et al., 2001), and has moderate solubility (blood:air partition coefficient of 68), all three pathways would be expected to contribute to its URT uptake and disposition.

The methodology for measuring uptake relies on the use of non-physiological flow conditions. Thus extrapolation of these uptake data to predict nasal scrubbing capacity of the rat or human under normal breathing conditions is difficult (Morris,

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**TABLE 1**

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<th>Exposure groups$^a$</th>
<th>25 ppm</th>
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$^a$ Uptake was measured continuously throughout the 60 min exposure under constant velocity inspiratory flow conditions at the flow rate indicated for the 25, 50, 100, or 300 ppm exposure groups. Values represent average uptake efficiency during the last 30 min of exposure and are expressed as percentage of the inspired concentration.

$^b$ Data are presented as mean ± SEM (n). Results were compared by repeated measures two-factor ANOVA, which detected a significant effect of flow rate \((p < 0.001)\), but no difference across exposure groups and no difference among exposure times (the repeated measure).
However, given that only moderate uptake efficiencies were observed in the current study, the data suggest that highly efficient uptake in either the rat or human nose is unlikely. Due to the simpler structure of the human nose compared to rat nose, it is anticipated that uptake may be less efficient in the human (Bogdanffy and Sarangapani, 2003; Frederick et al., 2002). More precise estimates of uptake efficiencies require the development and use of a mathematical model. By providing uptake data under well-defined conditions, the data generated in this report will be essential for development and/or validation of such a model (Morris, 1999).

The physiologically based pharmacokinetic model for URT vapor uptake that was developed in this laboratory (Morris et al., 1993) relates uptake efficiency to solubility, metabolism, and reaction rates. For a vapor with a partition coefficient like that of propylene oxide (68), this model predicts uptake efficiencies of 20 and 6% at constant velocity unidirectional flow rates of 50 and 200 ml/min, respectively, assuming there is neither metabolism nor direct reactivity. At these flow rates, propylene oxide uptake efficiencies of ~25 and 11% were observed. This comparison suggests that circulatory removal may be the predominant pathway responsible for steady state propylene oxide uptake,
but that other processes may serve to enhance uptake efficiencies.

At concentrations of 100 ppm or more, propylene oxide exposure resulted in significant depletion of nasal respiratory mucosal NPSH, providing strong evidence that direct reaction and/or conjugation of propylene oxide with glutathione and/or other NPSH groups occurred during the 1 h isolated URT exposure. After 1 h exposure at concentrations of 50, 100, 300, or 500 ppm nasal NPSH levels averaged approximately 75, 45, 35, and 15% of control levels (Fig. 2A). After repeated (6 h/day, 5 days/week, 4 weeks) whole body inhalation exposure to 50, 300, or 500 ppm nasal respiratory mucosal NPSH levels are depleted to approximately 39, 33, and 33% of control levels (Lee et al., 2000). Given the differing time courses of these experiments it is difficult to compare results directly; however, it appears there is reasonable concordance between the isolated URT and whole body exposure responses.

Quantitative examination of the NPSH data provides insights into several aspects of the disposition of propylene oxide within respiratory mucosal tissues. Glutathione constitutes approximately 60% of total nasal NPSH and it demonstrates biphasic turnover kinetics with fast and slow phase turnovers of 0.15 h⁻¹ and 0.02 h⁻¹, respectively in rat nasal respiratory mucosa (Potter et al., 1995). That even the “fast” turnover has a half-life of 4.4 h suggests there is unlikely to be much regeneration of GSH during the 1-h exposure. The other major contributor to nasal NPSH is cysteine, a precursor for GSH formation representing approximately 20% of total nasal NPSH (Potter et al., 1995). That NPSH levels were depleted to as low as 15% of control suggests that not only GSH, but also other non-protein sulfhydryl groups, were substrates for reaction with propylene oxide. Depletion of GSH precursors by propylene oxide would serve to limit the already slow capacity of nasal respiratory mucosa to regenerate GSH during exposure. At an inspired concentration of 100 ppm, approximately 50–90 nmol/min propylene oxide was removed from the airstream in the URT, corresponding to a total of 3000–5400 nmol propylene oxide removed/absorbed over the 60-min exposure. The total NPSH content of respiratory mucosa was ~80 nmol based on control values (Figs. 1, 2, and 4). Based on mass balance arguments, it seems likely that only a small fraction of the total absorbed propylene oxide was actually conjugated and/or reacted with nasal NPSH moieties unless they were either rapidly replenished from the bloodstream and/or the reaction took place within the vasculature itself. Thus, while reaction with GSH occurs, it does not appear to be a major contributor to overall uptake rates.

In the uptake study, the degree of respiratory mucosal NPSH depletion observed in the 50 and 200 ml/min groups did not differ significantly despite the fact that the delivered dosage rate was approximately twice as high in the 200 ml/min compared to the 50 ml/min group. The reasons for this are not clear, but may be due to the interanimal variability in NPSH levels and the slope of the concentration response curve. The SD for respiratory mucosal NPSH content was approximately 30% of the mean value, thus only relatively large changes in NPSH levels might be expected to be detected statistically among groups. The NPSH-propylene oxide concentration response curve is shallow, with only an ~15% change in respiratory mucosal NPSH level associated with a two-fold increase in inspired concentration (e.g., approximately 80 vs. 65% of control in the 50 vs. 100 ppm groups). In this context, the interanimal variability may have been sufficient to obscure an inspiratory flow rate dependence on respiratory mucosal NPSH levels.

Propylene oxide depletion of respiratory mucosa NPSH appeared to be faster and/or of greater magnitude than for olfactory mucosa NPSH. The greater degree of NPSH depletion in respiratory mucosa may reflect differences in delivered dose. The entire inspired airstream passes over the anterior respiratory mucosa lined tissues, whereas only approximately 15% of the inspired air passes into the posterior olfactory mucosal lined regions of the nasal cavity (Kimbell et al., 1993). In this regard it is interesting to note that in olfactory tissues both the rate of NPSH depletion was slow (Fig. 1B), and the degree of depletion was quite variable (Figs. 1B, 2B, and 3B). This suggests there is a close balance between the rate at which NPSH is reacted and the rate at which it can be replenished, perhaps from bloodstream-derived NPSH. Turnover of GSH in olfactory mucosa is slower than in respiratory mucosa, following monophasic behavior with a turnover rate of 0.02 h⁻¹ (Potter et al., 1995), thus regeneration of GSH from resynthesis is unlikely to occur during the 1-h exposure. Modelling of propylene oxide uptake kinetics might provide insights into the balance of these rates and into whether or not small changes in the fraction of air passing over the olfactory mucosa could exert a large influence on the rate of NPSH depletion by inspired propylene oxide.

The kinetics of propylene oxide uptake appear to be quite straightforward. Uptake remained constant throughout exposure, and was similar at all exposure concentrations up to and including 300 ppm. Were reaction with nasal NPSH to represent a quantitatively important pathway for propylene oxide clearance, it would be anticipated that uptake efficiencies should diminish during exposure as NPSH levels are depleted. However, reaction with NPSH is not likely to represent a quantitatively important clearance pathway because the total amount of nasal NPSH is quite small relative to the delivery rates of propylene oxide (see above). For a metabolized vapor, decreased uptake efficiencies would be anticipated at high exposure concentrations when the metabolic pathways become saturated (or pseudo-saturated, as is the case in GSH depletion kinetics). This has been observed for many vapors including styrene (Morris, 2000) and acetaldehyde (Morris and Blanchard, 1992; Stanek and Morris, 1999), but not for propylene oxide (Table 1). This may be due to the Km values of 2 mM or higher for nasal metabolism of propylene oxide via either GSH-tranferase or epoxide hydro-lase (Faller et al., 2001). Even at inspired concentrations of 300 ppm (~0.012 mmol/l air) tissue concentrations would not
be expected to exceed 0.8 mM (0.012 mmol/l × tissue:air partition coefficient of 68). Based on the high Km values as determined in vitro, saturation of this enzyme would not be anticipated at the exposure concentrations examined in the current in vivo study. Thus, the uptake behavior and the in vitro metabolic data are consistent.

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