Polycyclic aromatic hydrocarbons (PAH) are “reasonably anticipated to be human carcinogens” (1). Abundant evidence supports the role of PAHs as important causes of lung cancer and, perhaps, other cancers in smokers (2, 3). Many PAHs are potent locally acting carcinogens, and fractions of cigarette smoke condensate enriched in these compounds are tumorigenic. DNA adducts of benzo[a]pyrene (BaP), a prototypical PAH, have been identified in the lungs of smokers, and the spectrum of mutations seen in the p53 gene isolated from lung tumors is similar to that induced by PAH and their diol epoxide metabolites (4). PAHs are also believed to be causative agents for cancers of the lung in coke production workers and cancer of the skin in workers exposed to coal tar, shale oil, and soot (5, 6).

PAHs require metabolic activation to exert their carcinogenic effects (7). The principal route of metabolic activation of BaP that results in DNA adduct formation in human tissues proceeds by way of anti-7,8-dihydroxy-9,10-epoxy-7,8,9,10-tetrahydrobenzo[a]pyrene (BPDE; Fig. 1; refs. 8-10). A sizeable body of evidence supports this metabolic activation pathway as the major one for many other PAHs as well (9). There are also other mechanisms of BaP metabolic activation, but the evidence that these contribute to DNA adduct formation in humans is presently more limited (11, 12). Competing with PAH metabolic activation are a variety of detoxification pathways, including direct hydroxylation to form phenols, conjugation of epoxides and diol epoxides with glutathione, and glucuronidation of dihydrodiols (7). Multiple enzymes are involved in the metabolic activation and detoxification of PAH. Cytochromes P450 and epoxide hydrolase are involved in both activation and detoxification, whereas glutathione S-transferases and UDP-glucuronosyltransferases are involved mainly in detoxification (7). Many studies have investigated the role of polymorphisms in these enzymes as modifiers of cancer risk in people exposed to PAHs. The results of these studies have been somewhat inconsistent, although certain genotype variant combinations may lead to higher risk (13-16). Our goal has been to develop a cancer metabolite phenotyping approach, which would capture all genetic and environmental influences on PAH metabolism by actually measuring their metabolites in urine. We initiated this work by developing a method for analysis in human urine of r-1,2,3,4-tetrahydroxy-1,2,3,4-tetrahydrobenzo(a)pyrene (HOPhe; Fig. 1), but the levels of this metabolite were so low that the method would not be practical for application in epidemiologic studies (17). Therefore, we turned our attention to phenanthrene (Fig. 1), the simplest PAH with a bay region, a feature closely associated with carcinogenicity. Phenanthrene occurs in higher concentrations in the environment than does BaP, and its metabolites are more plentiful in urine (18). The metabolites of higher molecular weight PAHs are excreted mainly in feces, detracting from their use as biomarkers. Although phenanthrene is not considered to be carcinogenic, its pathways of metabolism are similar to those of BaP and other PAHs. Thus, as illustrated in Fig. 1, phenanthrene is metabolized to a diol epoxide in a manner similar to BaP (9, 19). Phenanthrene is also converted to phenanthrols (HOPhe) metabolically (20). The end product of the diol epoxide pathway is r-1,2,3,4-tetrahydroxy-1,2,3,4-tetrahydrophenanthrene (PheT; ref. 21). We propose that a ratio of PheT (as a marker of metabolic activation) to HOPhe (as a marker of detoxification) would be characteristic of a given individual’s ability to metabolically activate or detoxify PAHs. One major goal in this study was to compare levels of these metabolites in different groups. In this study, we investigated the longitudinal consistency of these metabolites over time in smokers and nonsmokers and compared their levels. Twelve smokers and 10 nonsmokers provided urine samples daily for 7 days, then weekly for 6 weeks. Levels of PheT, HOPhe, and PheT/HOPhe ratios were relatively constant in most individuals, with mean coefficients of variation ranging from 29.3% to 45.7%. There were no significant changes over time in levels of the metabolites or in ratios. These results indicate that a single urine sample should be sufficient when comparing phenanthrene metabolites in different groups. PheT/HOPhe ratios were significantly higher in smokers than in nonsmokers, showing that smoking induces the diol epoxide metabolic activation pathway of phenanthrene. This finding is consistent with previous studies indicating that inducibility of PAH metabolism contributes to cancer risk in smokers. (Cancer Epidemiol Biomarkers Prev 2005;14(12):2969–74)
to determine the longitudinal consistency of this ratio in a person. This would provide essential information with respect to the design of epidemiologic studies using this biomarker. A second goal was to compare the ratio in smokers and nonsmokers.

Materials and Methods

Study Design. The study was approved by the University of Minnesota Research Subjects’ Protection Programs Institutional Review Board Human Subjects Committee. First morning urine samples were collected from smokers or nonsmokers daily on days 1 to 7, then weekly on days 14, 21, 28, 35, 42, and 49 of the study.

Smokers were recruited through flyers posted at the University of Minnesota campus and near campus, and an advertisement in a hospital newspaper for a study of smokers who were not intending to quit. Interested participants called the Tobacco Use Research Center and were told that the study would involve submission of urine samples over a 7-week period to assess levels of cancer-causing agents. They were screened for current or recent bladder or urinary tract infection, and smokers had to smoke at least five cigarettes per day. Subjects who met the criteria (12 of 20 screened) were enrolled in the study. Before enrollment, subjects were asked to sign a consent form and then complete a demographic, smoking history, second-hand exposure, and physical health questionnaire.

Urine samples were dropped off at the Tobacco Use Research Center every 2 days during the seven-consecutive-day collection period and once weekly thereafter. Smokers were asked to record daily number of cigarettes they smoked during this urine collection period. At each visit, current use of medication was recorded, and alveolar carbon monoxide levels were assessed. Subjects were paid for each urine sample with a bonus for completing the study.

Nonsmokers were healthy volunteers recruited from Cancer Center employees, and urine collection procedures were similar to smokers. All subjects approached participated.

Analysis of Urine. Urinary PheT and 1-HOPhe, 2-HOPhe, 3-HOPhe, and 4-HOPhe were determined by gas chromatography-mass spectrometry as described previously, except that [D10]PheT was used as internal standard in the PheT analysis (20, 21). Creatinine was assayed by Fairview University Medical Center Diagnostic Laboratories (Minneapolis, MN) using Vitros CREA slides.

Statistical Analysis. In the statistical analysis, we included PheT, the end product of the diol epoxide metabolic activation pathway, 3-HOPhe, and total HOPhe. 3-HOPhe was chosen because the internal standard for the HOPhe assay is [ring-13C6]3-HOPhe, and measurement of 3-HOPhe is therefore highly accurate and precise. Total HOPhe (the sum of 1-HOPhe, 2-HOPhe, 3-HOPhe, and 4-HOPhe) indicates total HOPhe formation. In our hands, 9-HOPhe cannot be quantified accurately but has been reported to be a minor urinary metabolite by others (18).

Because the distribution of levels of PheT, HOPhe, and PheT/HOPhe ratios were positively skewed, we transformed all measurements to the log scale in our analysis and calculated geometric means.

Statistical analyses of PheT, HOPhe, and PheT/HOPhe ratio were based on ANOVA with repeated measurements. Calculations were done using SAS, version 8. These ANOVA analyses included one fixed factor (smokers versus nonsmokers) and one repeated factor (time: days 1-7, then weeks 2-7). We also included in each the interaction term between these two factors (smoking by time). The time effect would help to investigate the longitudinal consistency of these metabolites and their ratio. The fixed factor of smoking would help to investigate the effect of smoking on the diol epoxide pathway. The inclusion of an interaction factor would help to determine, if smokers and nonsmokers are different, whether their difference is constant over time.

Results

The 10 nonsmokers ranged in age from 23 to 50 years (mean ± SD, 35 ± 9 years); two were female. The 12 smokers smoked from 5 to 40 cigarettes per day (mean, 20 ± 10), had 0.5 to 20 pack-years of smoking (mean, 12 ± 9 pack-years), and ranged in age from 19 to 62 years (mean, 39 ± 12 years). Nine of the smokers were female.

Coefficients of variation (CV) for PheT, 3-HOPhe, total HOPhe and the ratios PheT/3-HOPhe and PheT/total...
HOPhe over the 49-day period for smokers and nonsmokers are summarized in Table 1. Variation in PheT levels was greater than that in levels of 3-HOPhe or total HOPhe. Five of 12 smokers and 2 of 10 nonsmokers had CV for PheT which exceeded 50%, whereas 3 of 12 smokers and 1 of 10 nonsmokers had CV of >50% for 3-HOPhe, and 3 of 12 smokers and 0 of 10 nonsmokers had CV of >50% for total HOPhe. Three of 12 smokers had >50% CV in PheT/3-HOPhe or PheT/total HOPhe ratios; these three individuals also had >50% variation in PheT levels. Overall CV ranged from 33.4 ± 14.3% (±SD; 3-HOPhe) to 40.5 ± 24.2% (PheT) in smokers and 29.3 ± 11.8% (3-HOPhe) to 43.0 ± 11.6% (PheT) in nonsmokers. CV for PheT/3-HOPhe and PheT/total HOPhe ratios were 37.3 ± 17.1% and 36.3 ± 18.4% in smokers, respectively, whereas the corresponding figures in nonsmokers for these two ratios were 44.0 ± 20.8% and 45.7 ± 20.3%.

Samples were taken daily for the first 7 days of the 49-day longitudinal study, then on days 14, 21, 28, 35, 42, and 49. CV for the first 7-day period for PheT/total HOPhe averaged 27.7 ± 13.9% in smokers and 35.0 ± 14.8% in nonsmokers. CV for days 14 to 49 averaged 38.7 ± 28.8% in

### Table 1. Geometric means of PheT, HOPhe, and PheT/HOPhe ratios over a 49-day period in smokers and nonsmokers

<table>
<thead>
<tr>
<th>CPD</th>
<th>PheT</th>
<th>3-HOPhe</th>
<th>Total HOPhe</th>
<th>PheT/3-HOPhe</th>
<th>PheT/Total HOPhe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD)</td>
<td>CV</td>
<td>Mean (SD)</td>
<td>CV</td>
<td>Mean (SD)</td>
<td>CV</td>
</tr>
<tr>
<td>Smokers</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>30</td>
<td>0.76 (0.21)</td>
<td>27.0</td>
<td>0.99 (0.22)</td>
<td>22.5</td>
</tr>
<tr>
<td>2</td>
<td>20</td>
<td>2.50 (0.62)</td>
<td>24.9</td>
<td>0.42 (0.12)</td>
<td>27.8</td>
</tr>
<tr>
<td>3</td>
<td>15</td>
<td>4.84 (3.35)</td>
<td>69.3</td>
<td>0.73 (0.44)</td>
<td>59.8</td>
</tr>
<tr>
<td>4</td>
<td>40</td>
<td>3.02 (0.81)</td>
<td>27.0</td>
<td>0.70 (0.56)</td>
<td>51.2</td>
</tr>
<tr>
<td>5</td>
<td>30</td>
<td>3.34 (0.42)</td>
<td>12.5</td>
<td>1.07 (0.16)</td>
<td>14.9</td>
</tr>
<tr>
<td>6</td>
<td>20</td>
<td>1.49 (0.29)</td>
<td>19.3</td>
<td>0.64 (0.15)</td>
<td>23.4</td>
</tr>
<tr>
<td>7</td>
<td>25</td>
<td>5.59 (3.28)</td>
<td>58.8</td>
<td>0.91 (0.31)</td>
<td>34.0</td>
</tr>
<tr>
<td>8</td>
<td>15</td>
<td>4.24 (2.42)</td>
<td>57.2</td>
<td>0.60 (0.16)</td>
<td>26.3</td>
</tr>
<tr>
<td>9</td>
<td>20</td>
<td>3.68 (0.76)</td>
<td>20.6</td>
<td>0.89 (0.29)</td>
<td>32.5</td>
</tr>
<tr>
<td>10</td>
<td>5</td>
<td>2.37 (1.68)</td>
<td>70.7</td>
<td>0.63 (0.23)</td>
<td>36.7</td>
</tr>
<tr>
<td>11</td>
<td>10</td>
<td>6.24 (4.90)</td>
<td>78.5</td>
<td>0.96 (0.50)</td>
<td>52.4</td>
</tr>
<tr>
<td>12</td>
<td>10</td>
<td>42.3 (8.37)</td>
<td>19.8</td>
<td>4.35 (0.83)</td>
<td>19.1</td>
</tr>
<tr>
<td>Overall*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonsmokers</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1.44 (0.63)</td>
<td>43.9</td>
<td>0.76 (0.27)</td>
<td>35.8</td>
<td>2.04 (0.89)</td>
</tr>
<tr>
<td>2</td>
<td>1.65 (0.62)</td>
<td>37.6</td>
<td>0.56 (0.098)</td>
<td>17.7</td>
<td>1.50 (0.26)</td>
</tr>
<tr>
<td>3</td>
<td>0.80 (0.32)</td>
<td>39.3</td>
<td>0.37 (0.086)</td>
<td>23.3</td>
<td>1.22 (0.29)</td>
</tr>
<tr>
<td>4</td>
<td>0.63 (0.26)</td>
<td>41.2</td>
<td>0.48 (0.25)</td>
<td>50.9</td>
<td>1.45 (0.65)</td>
</tr>
<tr>
<td>5</td>
<td>0.89 (0.24)</td>
<td>26.5</td>
<td>0.39 (0.12)</td>
<td>29.9</td>
<td>1.33 (0.48)</td>
</tr>
<tr>
<td>6</td>
<td>2.73 (1.33)</td>
<td>48.9</td>
<td>0.70 (0.20)</td>
<td>28.9</td>
<td>4.05 (0.93)</td>
</tr>
<tr>
<td>7</td>
<td>1.42 (0.53)</td>
<td>37.1</td>
<td>0.49 (0.06)</td>
<td>13.6</td>
<td>1.40 (0.29)</td>
</tr>
<tr>
<td>8</td>
<td>3.94 (2.19)</td>
<td>55.4</td>
<td>1.18 (0.23)</td>
<td>19.0</td>
<td>4.28 (1.76)</td>
</tr>
<tr>
<td>9</td>
<td>1.47 (0.99)</td>
<td>67.1</td>
<td>0.24 (0.069)</td>
<td>29.3</td>
<td>0.98 (0.26)</td>
</tr>
<tr>
<td>10</td>
<td>1.56 (0.52)</td>
<td>33.1</td>
<td>0.55 (0.24)</td>
<td>44.3</td>
<td>2.23 (0.91)</td>
</tr>
<tr>
<td>Overall*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Arithmetic means ± SD.

Abbreviation: CPD, cigarettes per day.

**Figure 2.** Individual variation in PheT/total HOPhe ratios in (A) 12 smokers and (B) 10 nonsmokers.
The results of this study show that although there is some
smokers and 52.5 ± 29.2% in nonsmokers. Similar results
were obtained for the other variables. There were no
significant differences in variability between the daily and
weekly sampling periods.

Variation in the PheT/total HOPhe ratio in each of the 12
smokers and 10 nonsmokers is illustrated in Fig. 2. Much of
the variation was accounted for by a few values (e.g., day 2 in
smoker number 7, day 42 in smoker number 8, or day 35 in
nonsmoker number 9). These outlier values were not due to
variation in the mass spectrometric analysis.

Overall, there were no significant variations in PheT,
3-HOPhe, total HOPhe, or either ratio with continuous time,
according to analysis by ANOVA for repeated measure-
ments. The results were the same in both smokers and
nonsmokers.

Correlations among PheT and HOPhe are summarized in
Table 2. Correlation coefficients for PheT versus 3-HOPhe
and PheT versus total HOPhe were generally in the range of
0.6 to 0.8 in smokers, with weaker relationships being
observed in nonsmokers. 3-HOPhe and total HOPhe were
highly correlated in both smokers and nonsmokers.

Comparisons of phenanthrene metabolites and metabolite
ratios over time in smokers and nonsmokers are presented in
Table 3. Levels of PheT and 3-HOPhe were significantly
higher in smokers than in nonsmokers, as was the ratio
PheT/total HOPhe. Data for the ratio PheT/total HOPhe in
smokers and nonsmokers are also illustrated in Fig. 3. The
ratio PheT/3-HOPhe was also higher in smokers than in
nonsmokers, but the difference barely missed significance.
Total HOPhe was not different in smokers and nonsmokers.
There was no relationship between number of cigarettes
smoked per day and levels of any of the analytes in the urine
of smokers.

Discussion

The results of this study show that although there is some
variation in urinary phenanthrene metabolite levels in an
individual over time, these variations are generally not large.
Mean CV for the phenanthrene metabolite ratios were 36.3% to
37.3% in smokers and 44.0% to 45.7% in nonsmokers. The
majority of the subjects (13 of 22) had CV values for the
metabolite ratios, which were <40% (Table 1). Similar results
were obtained for the metabolites PheT, 3-HOPhe, and total
HOPhe. There was no significant variation in any of the
metabolite ratios or metabolites over time. These results
indicate that when comparing phenanthrene metabolites or
their ratios between groups, such as smokers and nonsmokers,
a single sampling should be sufficient. Sampling in both
groups should be done at about the same time. When
comparing individual levels, multiple sampling would be
advisable if feasible.

Variations in PheT levels with time in a given individual
were generally greater than variations in 3-HOPhe or total
HOPhe. Thus, mean CV for PheT were 40.5% and 43.0%
in smokers and nonsmokers, respectively, whereas the corre-
sponding values for 3-HOPhe were 33.4% and 29.3%, and for
total HOPhe 34.9% and 31.8%. The greater variation in PheT
than 3-HOPhe or total HOPhe is not due to exposure
differences, because both metabolites are formed from
phenanthrene. Furthermore, there was no difference in CV
between smokers and nonsmokers, although smokers are
exposed to higher amounts of phenanthrene than non-
smokers. It is also not likely to be due to analytic differences
because analytic variation in the PheT and HOPhe assays
have been reported to be 16.2% for PheT and 5.7% to 22% for
HOPhe (20, 21). The most probable explanation is that
multiple enzymes are involved in PheT formation. Levels of
PheT will be influenced by cytochrome P450s, epoxide
hydrolases, UDP-glucuronosyl transferases, glutathione
S-transferases, and possibly other enzymes (7, 22). In
contrast, formation of HOPhe is catalyzed predominantly by
cytochrome P450s (19). There could be diverse genetic,
environmental, and dietary influences on the activity of these
enzymes, thereby leading to more variation in PheT levels
than in HOPhe. A further consequence of the smaller
variation in HOPhe than PheT was the strong correlation
between 3-HOPhe and total HOPhe, whereas the correlation
between PheT and phenanthrols was weaker.

Levels of urinary PheT in an individual result from exposure
plus metabolic activation of phenanthrene. Because
phenanthrene always occurs in a mixture with other PAH and
because many of these carcinogens are metabolically activated
by the same mechanism that produces PheT, levels of PheT
should indicate exposure plus metabolic activation of PAHs.
Our main interest is to detect those individuals who are

Table 2. Correlations between log-transformed phenanthrene metabolite values over 49 days, in smokers and nonsmokers

<table>
<thead>
<tr>
<th></th>
<th>Smokers</th>
<th>Nonsmokers</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>PheT vs 3-HOPhe</td>
<td>r 0.76</td>
<td>0.73</td>
<td>0.70</td>
</tr>
<tr>
<td>P</td>
<td>0.004</td>
<td>0.007</td>
<td>0.01</td>
</tr>
<tr>
<td>PheT vs total HOPhe</td>
<td>r 0.75</td>
<td>0.62</td>
<td>0.60</td>
</tr>
<tr>
<td>P</td>
<td>0.005</td>
<td>0.03</td>
<td>0.04</td>
</tr>
<tr>
<td>3-HOPhe vs total HOPhe</td>
<td>r 0.95</td>
<td>0.73</td>
<td>0.94</td>
</tr>
<tr>
<td>P</td>
<td>&lt;0.0001</td>
<td>0.006</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Table 3. Comparison of phenanthrene metabolites in smokers and nonsmokers over a 49-day period

<table>
<thead>
<tr>
<th>Metabolite</th>
<th>Smokers</th>
<th>Nonsmokers</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>PheT*</td>
<td>3.74 ± 3.85</td>
<td>1.44 ± 0.97</td>
<td>0.0073</td>
</tr>
<tr>
<td>3-HOPhe*</td>
<td>0.87 ± 0.57</td>
<td>0.52 ± 0.27</td>
<td>0.023</td>
</tr>
<tr>
<td>Total HOPhe</td>
<td>2.67 ± 1.57</td>
<td>1.81 ± 1.04</td>
<td>0.098</td>
</tr>
<tr>
<td>PheT/3-HOPhe</td>
<td>4.30 ± 3.25</td>
<td>2.76 ± 1.70</td>
<td>0.062</td>
</tr>
<tr>
<td>PheT/total HOPhe</td>
<td>1.39 ± 0.29</td>
<td>0.78 ± 0.10</td>
<td>0.013</td>
</tr>
</tbody>
</table>

*pmol/mg creatinine.
susceptible to PAH carcinogenesis at a given level of exposure. The PhET/3-HOPhe or PhET/total HOPhe ratios should correct for exposure and give a more precise indication of individual differences in metabolism. Levels of PhET and the ratios both should be applicable in epidemiologic studies: PhET as a measure of exposure plus metabolic activation and ratios as an indication of differences in metabolism at a given level of exposure. It is not clear at present which measure may provide a better indication of cancer susceptibility upon PAH exposure.

A potentially important finding of this study was the significantly higher PhET/total HOPhe ratio in smokers than in nonsmokers (Fig. 3). It is well established that cigarette smoking induces cytochromes P450 1A1, 1A2, and 1B1 through interactions of PAHs, and possibly other cigarette smoke constituents, with the ary hydrocarbon receptor (AHR; refs. 23-28). Approximately 10% of people have a high AHR inducibility phenotype (25, 26). A number of studies have associated this phenotype with a higher risk for lung cancer and other cancers in tissues, which come in direct contact with cigarette smoke, although there seem to be many confounding factors, and the results are not entirely consistent (23-26). Cytochromes P450 1A1, 1A2, and 1B1 are involved in both the metabolic activation and detoxification of PAHs (29-35). One series of studies showed a relationship between induction of these enzymes in smokers and BPDE-DNA adducts in the lung (36, 37). However, to our knowledge, there have been no previous studies which have examined the consequences of induction of cytochromes P450 1A1, 1A2, and 1B1 by cigarette smoke with respect to activation versus detoxification of PAHs in humans. Our results show that the diol epoxide metabolic activation pathway of phenanthrene is induced to a greater extent than the phenol metabolism pathway in smokers (Fig. 3). This finding is consistent with the proposed relationship between P450 1A1 and 1B1 induction and increased cancer risk. The greater induction of the diol epoxide than the phenol metabolism pathway is logical because P450 1A1, 1A2, and 1B1 are involved in two steps in diol epoxide formation but only one step in phenol formation (Fig. 1). In addition, some studies indicate that epoxide hydrolase, which is also involved in diol epoxide formation, is induced in smokers, but others show no change (38-41).

A limitation of this study was its relatively small size, involving only 12 smokers and 10 nonsmokers. This was dictated by the multiple sampling (13 per individual) and the relative complexity of the separate analyses for PhET and HOPhe. We are developing more rapid methods of analysis of these metabolites, which will facilitate larger studies. A second limitation is that phenanthrene is being used as a surrogate for carcinogenic PAHs and urinary metabolites as a surrogate for cellular changes relevant to cancer. We do not know if high PhET levels indicate correspondingly high levels of formation of BPDE and BPDE-DNA adducts in lung or other tissues. This is currently under investigation.

In summary, the results of this study indicate that levels of the phenanthrene metabolites PhET and HOPhe in urine are relatively constant over time in a given individual, supporting their use as biomarkers of PAH metabolism. We also showed that the diol epoxide metabolic activation pathway of phenanthrene is induced in smokers, consistent with an important role for PAHs in smoking-induced cancer.

Acknowledgments
We thank the subjects for participation in this study and Bob Carlson for editorial assistance.

References


Longitudinal Study of Urinary Phenanthrene Metabolite Ratios: Effect of Smoking on the Diol Epoxide Pathway

Stephen S. Hecht, Menglan Chen, Andrea Yoder, et al.