Published in final edited form as:

Curr Drug Metab. 2018 ; 19(1): 3–46. doi:10.2174/1389200219666171207123939.

Development and Uses of Offline and Web-Searchable Metabolism Databases - The Case of Benzo[a]pyrene

Slobodan P. Rendic^{1,*} and F. Peter Guengerich²

¹Independent scientist, Haulikova 6, Zagreb, Croatia

²Department of Biochemistry, Vanderbilt University School of Medicine, Nashville, Tennessee 37232-0146, United States

Abstract

The present work describes development and use of offline and Web-searchable human and other species metabolism databases. A search of the databases presented will produce basic information on metabolic reactions or transporter systems published on specific drug or other chemical, kinetic values, as well as structure of the metabolites. In addition, searching enables comparison of the data between different species models. The data cover time the period until 2008, and the current Web-searchable database [19] is updated quarterly each year and over the period until October 2017. Users of the databases might find occasional discrepancies between the data searched, *e.g.* data on metabolic activations as presented in Table 6. This is because the data were collected from different literature sources over the time of collection. The data searched may find their application in prediction and interpretation of the metabolism of drugs and other chemicals, drug design, and development, as well as in clinical and toxicological studies. Application of data searching to the study of xeno- or endobiotics metabolism is illustrated by those searched for the properties of the known environmental carcinogens benzo[a]pyrene (B[a]P) and its metabolites covering the period until the year 2008. The results of the data analysis show higher activity of P450 1A1 for metabolic activation of the (–)- isomer, while P4501B1 exerts higher activity for the (+)- isomer of *trans*-7, 8-dihydroxy-7,8-dihydrobenzo[a]pyrene (*trans*-B[a]P-7,8-diol). P450 1A2 showed equally low activity in the metabolic activation of both isomers (Tables 2 and 3). The current Web-searchable metabolism database contains 125,359 entries.

Keywords

P450; CYP; transporters; metabolism databases; Web-database; benzo[a]pyrene; metabolic activation; xenobiotics; endobiotics

* Address correspondence to this author at Haulikova 6, HR 10 000 Zagreb, Croatia; Mobile: +385917393456; slobodanrendic@yahoo.com.

DEDICATION

This review is dedicated to the memory of Vjeka Rendic who passed away in 2014. Vjeka, the wife of one of the authors, was of great support to him during his long term academic, research, and publishing activity in the field of P450s.

The author declare no competing financial interest

1. INTRODUCTION

Development of the metabolism databases was prompted by the large amount of data on metabolism of xenobiotics and endobiotics catalyzed by cytochrome P450 (P450, CYP) enzymes published after year 1990. The initial data collection was focused on the interaction of the compounds with human P450 enzymes and transporters. At a later stage the database development continued by addition of data obtained using non-human species models, kinetic and structural information on the substrates and metabolites.

Cytochrome P450 enzymes catalyze oxidative, peroxidative and reductive transformations, and some P450s act as isomerases, reductases, dehydratases, or NO synthases (nitric oxide synthases); they catalyze oxidative cleavage of esters as well. Xenobiotics, which are substrates of the enzymes, are both synthetic chemicals (i.e. drugs, pesticides, and other chemicals including carcinogens) and natural compounds. Substrates also include endobiotics of great physiological importance such as steroids, fatty acids, retinoids, eicosanoids, and lipid hydroperoxides. Although P450 enzymes generally transform xenobiotics to less toxic, and more water-soluble products, the reactions frequently involve formation of reactive intermediates or, in a few situations, allow the leakage of free radicals capable of causing toxicity, e.g. CCl₄. The significance of the human P450 enzymes in drug metabolism has been reviewed in details in previous reviews [1–4]. The roles of the transporters, which (depending on the site of expression) may enhance or limit the absorption or excretion of drugs and other xenobiotics from an organ or tissue and have additional effects on the biological activities of drugs/xenobiotics, have also been reviewed [5,6]. In addition to a great number of compounds used as drugs or being found in the environment, and influencing the activity and/or expression of the cytochrome P450 enzymes and transporters [1,2,5], the effects of diseases and environmental factors and environmental factors—including ionizing radiation, UV, γ -rays, X-rays—are also of interest and have been reviewed [7,8]. Such factors can have profound effects on enzyme activity and expression and therefore also on the final biological activity, efficacy, and safety of drugs and other chemicals. It was reported, for instance, that irradiation, alone or in combination with specific drugs (e.g., anticancer drugs) might result in a significant change of therapeutic outcome or resistance to a drug might occur [8]. Such effects might contribute to drug-drug, drug-chemical, or chemical-chemical interactions by modifying the disposition of xeno- and endobiotics, and consequently their fate in the body. In addition, the role of individual enzymes in carcinogen metabolism has been studied extensively, and roles of many human P450s in carcinogen activation have been characterized. The effects might contribute to *drug-drug*, *drug-chemical*, or *chemical-chemical* interactions by modifying the disposition of xeno- and endobiotics, and consequently their fate in the body. In addition, the role of individual enzymes in carcinogen metabolism has been studied extensively, and roles of many human P450s in carcinogen activation have been characterized [9–12]. Studies with P450s led the way, and similar approaches have been used with other enzymes known to have roles in the metabolism of xenobiotics chemicals [13,14]. Research in this area has been important in several applied disciplines and approaches. These include molecular epidemiology, which is an attempt to relate risk from carcinogens to the enzymes present in an individual [15–17]. In our previous report [18], data collected for the ADME database

[19] were used to analyze the fractions of the different enzymes involved in activation reaction of carcinogens. This analysis showed that the metabolism—and especially the bioactivation—of carcinogens is dominated by cytochrome P450 enzymes (66% of bioactivations). Within this group, six P450s—1A1, 1A2, 1B1, 2A6, 2E1, and 3A4—accounted for 77% of the P450 activation reactions. The roles of these P450s can be compared with those estimated in similar comparisons for drug metabolism [20] and should be considered in issues involving enzyme induction, chemoprevention, molecular epidemiology, inter-individual variations, and risk assessment. The approach used in the analysis is illustrated by metabolism and activation of well known environmental carcinogen benzo[*a*]pyrene and its metabolites (Fig. 1) [21–25].

The present work describes the time course of development of offline and Web-searchable metabolism databases covering data obtained by using human and other species as models. The intent of creating the databases was to provide quick and accurate approach to both previously and currently published data on the metabolism of xeno- and endobiotic substances to be applied both in science (drug development, environmental, toxicological and clinical studies) and even in everyday life to assist therapy and was prompted by the rise of data published in this scientific field during the years after 1990. The approach used for data collection and the results obtained by searching the databases is exemplified by the data collected benzo[*a*]pyrene (B[*a*]P) covering the time period until the year 2008. The results obtained on this example compound led to the conclusion that P450 1A1 exerts that higher activity for metabolic activation of the (–)- isomer of the compound, while P4501B1 exerts higher activity for the (+)- isomer of trans-7, 8-dihydroxy-7,8-dihydrobenzo[*a*]pyrene (*trans*-B[*a*]P-7,8-diol). P450 1A2 showed equally low activity to metabolically activate both isomers tested. Data on the database use show their application in fields such as computer assisted drug design and development, optimization of clinical therapy, and toxicology.

The authors of the paper have experience working on the subjects covered by the paper as one of them (S. P. Rendic) collected the data that were organized as offline Excel format databases (from 1990 until 2008) and included later on into Web-searchable database by Gentest Corp., USA and Fujitsu Kyushu Systems Ltd. JAPAN (FJQS) (Part 5). After the year 2008 the data collection continued at Fujitsu Kyushu Systems Ltd. JAPAN (FJQS) and Poland (FQS Poland Sp. zo. O). The scope of research of co-author (F.P. Guengerich) is mechanisms of activity of P450 enzymes, and biotransformation and toxicity of polycyclic aromatic hydrocarbons including benzo[*a*]pyrene. The data collected through the time of collection are available to the scientific community either through publishing activities of the authors [1–4,7,8], or were made available as open-access free Web-searchable databases as discussed in the paper (Part 5). After the year 2003 the ADME database became Web-searchable through subscription at the Fujitsu Kyushu Systems Ltd. Japan (FJQS) website [19].

2. TABULAR PRESENTATION AND SEARCHING FOR DATA

Searches for data were done using the PubMed database, accessing the Medline database of references and abstracts. Key words used for searching literature data covered major properties such as P450s, CYP, transporters, kinetic parameters, human data, other species,

data, activation, *etc.* In addition to the published data, additional data presented at scientific conferences as posters (i.e., ISSX international and regional conferences) are included in the database. No statistics were done regarding inclusion or rejection of the data. In the latter stages the existing literature and the original papers were systematically analyzed, extracting the data for introduction to the offline and online metabolism databases and related to the metabolism of chemicals and other factors that were shown to have influences on the enzyme activity (such as illnesses, radiations, environmental factors, physiological stress). The literature sources used were original, as well as review papers covering the publishing period beginning with the year 1976. The data presented in tables are formatted in following columns: 1. Enzyme; 2. Compound/metabolite; 3. Reaction(s) catalyzed by the enzyme(s); 4. Type of interaction; 5. Remarks about effects to additionally characterize the process; 6. References for the enzyme(s). In kinetic database data are formatted in columns: 1. Enzyme; 2. Model used; 3. Substrate; 4. Inhibitor/ligand; 5. K_m ; 6. V_{max} or k_{cat} ; 7. Enzyme efficiency; 8. IC_{50} ; 9. References. As experimental results may depend upon the model used this information is added.

3. INITIAL P450 METABOLISM DATABASE, 1989/1990

Initially collected data on interaction of xeno- and endobiotics with cytochrome P450 enzymes for the year 1989/1990 are presented in Table 1. The data presented were obtained by using both human and animal experimental models and show that B[a]P is predominantly activated to toxic metabolites by Family 1 P450s.

It should be emphasized that since 1990 information on P450 enzymes, when interacting with xeno- and endobiotics, accumulated rapidly and in some cases data were modified. This is illustrated with data on interactions of benzo[a]pyrene (B[a]P) as a substrate of P450 enzymes presented in Table 2. Analysis (Table 2) refers to those data collected in the period from the year 1978–2008, confirming the major role of Family 1 P450s (1A1, 1A2, 1B1) in the metabolism of B[a]P and also including additional enzymes such as P450 2C8, 2C9, 2C19, 2D6, 2E1, and 3A4, which participate in the metabolism and activation of the compound. Of the total of 63, 51 entries (Table 2) are related to metabolism of B[a]P catalyzed by P450 1 Family. Activation to potentially toxic metabolites was predominately ascribed to the activity of P450 1A1, 1A2, and 1B1 enzymes and only minor data are ascribed to P450 subfamilies 2C (6 entries), 2D (1 entry), and 2E and 3A (2 entries each). Of the latter group of enzymes, P450 3A4 and 2E1 also activated B[a]P to toxic metabolites.

In addition, B[a]P is described as an inhibitor of P450s 1A1, 1A2, 1B1, 3A4, and 19A1 (steroid aromatase) and an inducer of P450 1A1, 1A2, and 1B1 (Table 2).

4. HUMAN P450 AND TRANSPORTER METABOLISM DATABASE DEVELOPMENT, 1990–2002

As research in the field of metabolism of xeno- and endobiotics after the year 1990 expanded, interest developed for providing the possibility of quick and systematic approaches to the published data. Thus, additional collection of the data was necessary regarding human P450s and, in addition, human transporter metabolism data. The collective

information on human P450 metabolism data was presented in a tabular format as a part of the review published in 1997 [1]. Publishing of this review was strongly supported by the late Dr. Frederick J. Di Carlo, prominent toxicologist, who was executive editor of the journal *Drug Metabolism Reviews* and one of the founders of the scientific society ISSX (International Society for the Study of Xenobiotics). The next update of the data collected was published in 2002 in which we discussed data collection, interpretation, and presentation of the experimental results [2]. The data presented in these two publications were formatted in an Excel format searchable database. The offline searchable database was constructed by the author's son Borut Rendic, who was educated in informatics at the Faculty of Electric Engineering and Informatics of the University of Zagreb. The searchable data output of the Excel database was presented and sorted in tabular format in the following order: A. Species, B. Enzymes; C. Category (therapeutic/chemical); D. Subcategory; E. Chemical, Drug (interacting with the enzyme/transporter), F. Structure (when published), G. Reaction(s) (catalyzed by the enzyme); H. Type of interaction with the enzyme/transporter (substrate, inhibitor, inducer...), I. Remarks, J. Reference(s). Part of the offline database is presented in Table 2, presenting search results for metabolism of B[a]P, catalyzed by P450 enzymes.

The results presented in Table 2 were obtained by searching different columns for selected parameters:

Human (parameter selected in column A – Species)

CYP1 Family (parameter selected in column B- for selected Enzyme)

Other chemicals (parameter selected in column E- Category)

and for

Activation“ (parameter selected in column G- Reaction).

The Excel formats of the databases have been updated continuously by amending data already present (for instance, by adding additional reaction(s), changing attributes such as major/minor reaction/transporter, potent/less potent inhibitor/activator etc.), by adding additional references, and/or by adding new information. In some instances, the previous information had to be deleted and/or changed in accordance with the latest published information.

The data presented in Tables 2 and 3 were collected from 5,155 references covering the period up to the year 2008. At that time the Excel formatted database contained 22,662 entries, including 101 entries with data from other species models than human. When searching the database only for compounds in the group of “*Other chemicals*” (this group consisted of environmental chemicals such as polycyclic aromatic hydrocarbons (PAHs), aromatic hydrocarbons, aromatic amines, tobacco-specific nitrosamines, complex environmental pollutants mixtures, imidazoles, and others and excluded drugs, physiological and natural compounds, and pesticides) the number of entries attributed to metabolic activation of “*other chemicals*” was 863, which is about 3.8% from a total of 22,662 entries. When “*activations*” was searched for the same group of compounds (“*Other chemicals*”), taking into account data collected up to the year 2001 (in that time database contained in

total 4,644 entries collected from 1826 references), 247 entries were ascribed to metabolic activations, which is ~1.2% of total entries in the database. This result shows that the number of entries attributed to metabolic activations increased slightly (from 1.2% to 3.8%) of the total number of the data present in the database (from 4,644 to 22,662).

The data in Table 3 present examples of the kinetic properties of benzo[*a*]pyrene metabolism by human P450s. In addition to the kinetic data, comments on potential toxicity by metabolic activation of the compound and metabolites are also provided. These data are used as examples of information that can be obtained when searching for kinetic properties of the compounds and metabolites. The data in Table 3 cover the collection period up to 2008, collected by the author (S. P. Rendic) and they do not cover the data published after year 2007 which are available in the current Web-searchable metabolism database [19]. Kinetic database contains also information on the experimental model used as this might influence the outcome of the results. The data in Table 3 show that ratio of $V_{\max}$ to K_m for the formation of *trans*-7,8-dihydroxy-7,8-dihydrobenzo[*a*]pyrene by recombinant human cytochrome P450 1A1 and 1B1 was 3.2-fold higher with P450 1B1 than with P450 1A1. The results also show higher activity of P450 1A1 for metabolic activation of the (–)- isomer, while P4501B1 exerts higher activity for the (+)- isomer of *trans*-7, 8-dihydroxy-7,8-dihydrobenzo[*a*]pyrene (*trans*-B[*a*]P-7,8-diol). P4501A2 showed equally low activity to metabolically activate both isomers [26, 27].

Searchable information for a specific compound, such as presented for B[*a*]P and metabolites, gives researchers the possibility to predict drug-drug and/or drug-chemical interaction potentials that might result in lack of response to the therapy or toxic actions.

5. WEB-SEARCHABLE HUMAN P450 AND TRANSPORTER METABOLISM DATABASE, 1998-

The first free web-searchable P450 metabolism database (1998) was made possible through cooperation with Gentest Corp., USA. (Fig. 2), supported by Dr. Charles Crespi. The “Human P450 Metabolism Database” was free and Web-searchable at the Gentest Corporation website www.gentest.com until the end of 2003. The database contained a collection of information on human cytochrome P450 metabolism. Professionals from different disciplines searched the database, *e.g.* pharmaceutical company researchers, family physicians, clinical and environmental toxicologists, academic, pharmacoinformatic and drug discovery professionals, clinical pharmacologists, and even people managing their everyday food intake.

From 2000–2003 the Human P450 Metabolism Database became a part of the Webdatabase system of Fujitsu Kyushu System Engineering Inc., Computer Chemistry Section, Fukuoka, Japan, and a part of the Japan Biological Informatics Consortium (JBIC) project as the JBIC Biotechnology database. The project was established by number of companies and institutes in Japan and supported by the Japanese Government to promote the application of informatics in the biotechnology and biotechnology informatics field. Searches of the JBIC Biotechnology Web database were made possible through subscription for companies, but were at that time free for academics at <https://jbic12jbic.or.jp/dmddb/index.html>.

The combined JBiC-Web fully searchable database provided information contained in all databases created off-line (P450-, transporter-, structural- and kinetic-database) and was evaluated highly by JBiC, Japanese pharmaceutical industries, and the Japan Pharmaceutical Association. When the JBiC project was terminated (after the year 2003) the ADME database became World Wide Web-searchable through subscription [19]. The current ADME database [19] contains searchable information on metabolic properties of drugs and other chemicals obtained with both human and other species models. The database contains information on cytochrome P450 and other enzymes (including esterases (ESs), UDP-glucuronosyltransferases (UGTs), sulfotransferases (SULTs), glutathione S-transferases (GSTs), flavin-containing monooxygenases (FMOs), aldo-keto reductases (AKRs) and others) participating in xeno- and endobiotics metabolism. Development of the database system was presented at several ISSX Meetings (Indianapolis 2000, Orlando 2002, Dijon 2003, Providence 2003, Vancouver 2004, Maui Hawaii 2005, Sendai 2007).

The database is updated quarterly during the year and the latest update of October 2017 [19] contains 125,359 entries of which 75,026 entries are related to the interactions with P450 enzymes (Table 4) [19].

6. APPLICATIONS AND EXAMPLES OF THE USE OF THE DATABASE

The information presented here provides information on chronological development, the current state of art, and use of data available for search at the Web metabolism database [19]. The data collected are intended for use by researchers working in the field of metabolism of drugs and other chemicals, including toxicological and clinical applications. The Web search ensures quick and accurate updated information and, besides information on reactions catalyzed by the metabolic enzymes, it provides also information about transporters and drug-drug and drug-other chemicals interactions, kinetic information, and structures of the compounds and metabolites. The data are collected by extensive keyword literature searches using the PubMed database, accessing the MEDLINE database of references and abstracts. In addition, together with the searched information, provided is direct link to the publication which is the source of information.

6.1. Searching the Web database

6.1.1. Search types that can be performed

- Basic search by selection keywords from a list;
- Advanced refine searches by customizing the search conditions;
- Free text search through all search fields for any given keyword/s;
- Structure search for compounds that are similar or containing the given input structure;

6.1.2. Provided search fields

- Drug category/subcategory;
- Drug/compound name;

- Interaction by type (*i.e.* substrate/inhibitor/mechanism based inhibitor/inducer/ etc.);
- Reaction type (this searching is possible by using Advanced Search);
- Remarks (such as mechanism-based inhibitor, potent/weak inducer/inhibitor, activator/stimulator, major/minor metabolite, activation and others);
- Species (human, mouse, rat, dog, yeast, fungi, bacteria, rabbit, and others);
- Drug/compound metabolizing enzyme / transporter participating in the reaction;
- Metabolic level (major/minor metabolite, major/minor enzyme, high/medium/low K_m , high/medium/low efficiency/activity).

7. DISCUSSION

As presented in Table 1 in the year 1989/90 limited metabolic data was available about interactions of xeno- and endobiotics with particular P450 enzymes. In comparison with these data, as presented in Table 4, the current Web metabolism database provides metabolic information contained in more than 75026 entries related to interactions of xeno- and endobiotics with P450 enzymes (Table 4). Table 5 gives information on the number of entries related to interactions of B[a]P and its metabolites as substrates, inhibitors and/or inducers of P450 enzymes in humans and other species, as well as of those with other enzymes (*e.g.* AKRs, EH, UGTs, SULT).

The numbers show significant increase from 2008 to 2017. For human P450 data the number of entries related to B[a]P metabolism increased from 201 to 331, and data entries for the other enzymes from 3 to 21. The data in Table 6 show the number of entries related to B[a]P metabolism with human metabolism enzymes as substrates, inhibitors, inducers, as well as those having the potential to result in activation to toxic species. In some examples activation is described as both potent and weak activation (for example for P450 1A1 and 1B1, Table 6). This discrepancy is caused as data were collected from experiments using different experimental models.

The metabolic pathway for B[a]P is very complex (Fig. 1) and has been subject of extensive research over time and extensively discussed in research papers, reviews, and the references cited the published papers. In the present discussion, we refer to some recently published reports [28,29,30]. As presented in Tables 1–6 and Fig. 1 B[a]P is a substrate in oxidative reactions catalyzed by several enzymes (P450s, peroxidases, and AKR enzymes). Being a substrate in oxidative reactions, B[a]P is converted to toxic products exerting different toxicity potentials and this might occur through several mechanisms. It was reported that B[a]P-7,8-dihydrodiol and B[a]P-9-ol, which are precursors of B[a]P toxic metabolites, are mainly formed by CYP1A1, 1B1, and (to a lesser extent) by CYP2C19 and CYP3A4. In contrast, the formation of B[a]P-3-ol is most efficiently catalyzed by CYP1A1 and 1B1, but CYP2B6, 2C9, 2C19, and 3A4 also partially contribute to its production [30]. The enzymes converting B[a]P to toxic species might be strongly induced or inhibited by many different chemical agents, including the compound itself (Tables 1 and 2) through the action of the aryl hydrocarbon receptor (AhR) [31]. Therefore, compounds acting as AhR activators or

inhibitors might potentially enhance or lower the toxicity of B[a]P by induction or inhibition of the activating enzyme activity. Thus, the toxicity and the ratios of metabolites formed of B[a]P *in vitro* might be different depending of the experimental model and the procedure used, and *in vivo* product distribution might depend on exposure of an organism to variety of environmental impacts, as well as to its physiological state (*e.g.* illness, stress) [7,8,32,33].

As shown in Fig. 1, of the four B[a]P-7,8-dihydrodiol stereoisomers that might be formed during its metabolism, (+)-*anti* (*trans*)-diol-B[a]P-epoxide appears to be the most mutagenic [24]. It was concluded that the various enantiomeric components of dihydrodiol products formed in the metabolism of polycyclic aromatic hydrocarbons (PAHs) including B[a]P, were formed due to the combined effect of stereoselectivity of the P450s and regioselectivity of epoxide hydrolase [34]. P450 1A1 and 1A2 enzymes have the capacity to metabolize B[a]P to both *cis*- and *trans*-7,8-dihydrodiol isomers, and P450 1A1 has a major role in activation of B[a]P to carcinogenic B[a]P-diol epoxide(s) [35]. The data presented in Table 6 are consistent with this discussion and with data presented in Table 1 showing that enzymes belonging to cytochrome P450 1 family (P450 1A1, 1A2, and 1B1) are the major enzymes responsible for metabolic activation of B[a]P to toxic products. Discrepancies in the information in Table 6 (potent or weak activation) is the consequence of collecting the data which used different models through the time of collection. The data presented in Tables 2 and 3 show, in addition, higher activity of P450 1A1 for metabolic activation of the (–)- isomer, while P450 1B1 exerts higher activity for the most toxic (+)- isomer of *trans*-7, 8-dihydroxy-7,8-dihydrobenzo[a]pyrene (*trans*-B[a]P-7,8-diol). P450 1A2 showed equally low activity in activating both of the isomers. However, it has also to be considered that AKR enzymes may effectively compete with P450 1A1/1B1 for B[a]P *trans*-dihydrodiol activation to a potentially toxic *o*-quinone as studied in human lung cells [22,36].

As already discussed in the Introduction section, the data collected were used to analyze effects of different factors on drug metabolism that might be of clinical and/or toxicological interest. For instance, analysis of the effects of diseases and different environmental factors on human cytochrome P450 enzymes and transporters revealed inconsistency of the reported results, makes it difficult to reach conclusions. However, some results could link causality with changes in gene expression. For instance, the increases in mRNA and protein expression of glucose transporters (GLUT) were suggested as markers of the aggressive biological potential of tumors (associated with poor survival of patients). It was suggested that inhibition of the up-regulation of these transporters might be a promising tool that would be beneficial in cancer prognosis and therapy. Similarly, increases in expression levels of P450s 1B1 and 2J2 in tumor cells and tissues (these enzymes are otherwise not present or present at very low levels in normal tissues) have been suggested as tumor markers in the diagnosis and prognosis of different malignancies. Although in some cases inconsistent results have been obtained, over-expression and increased functional activity of transporters such as MRPs (in particular MRP1, MRP2, and MRP3), P-gp (MDR1), LRP, and BCRP1 in tumors have been suggested as predictors and as participants in acquired multidrug resistance *in vivo*. On the other hand, enhanced or lowered expression and/or activity of P450 enzymes in some diseases could result in clinically significant drug interaction potential, resulting in unfavorable clinical outcome or increased drug/chemical toxicity. Some examples include increased expression of P450 2E1 due to alcohol in healthy subjects

and decreased enzyme expression in alcoholic liver disease (ALD), increased P450 2E1 expression in livers of transplant patients, high expression of P450 3A4 enzyme in lymphoid carcinoma (proposed as a useful predictor of poor response to the standard peripheral type lung cancer (PTLC) chemotherapy), and high expression of P450 3A enzymes in osteosarcomas (suggested as a predictor of metastasis and poor prognosis) [7]. The subject of another report using collected data was analysis of the effects of ionizing radiation (i.e. γ -rays, α - and β -particles, high-frequency ultraviolet radiation, X-rays, and fast neutron irradiation, and contamination with radioactive particles) and non-ionizing radiation (UVA, UVB, and UVC) on cytochrome P450 and other drug metabolizing enzymes and transporters [8]. The analysis showed that (although also in this case some inconsistent results and conclusions have been obtained) the increases in mRNA and/or protein expression of transporters (P-gp, Mrp1, LRP) by γ -rays or ionizing radiation may link causality with changes of gene expression. For instance, increased P-gp, and Mrp1 or Mrp2 mRNA and/or protein expression was associated with increased resistance to anticancer drugs resulting in the development of highly resistant irradiated cancer cell phenotypes following (fractionated) ionizing radiation (total dose up to 75 Gy) using human models. Interestingly, in a murine model (total dose of 60 Gy) P-gp (Mdr1a and Mdr1b) mRNA was not detectable or was reduced, but protein expression increased three-fold. In a human model, expression of mRNA and protein was tissue dependent (*i.e.* in irradiated colon cancer cell lines no increase of MDR1, MRP1, or LRP mRNA expression was observed but a large increase in protein level was observed). On the other hand, in irradiated breast cancer cell lines both mRNA expression and protein levels of the transporters were increased. In both models, murine and human, increased protein levels resulted in significant resistance to anticancer drugs. This result raises the suggestion that functional analysis should be preferred when testing effects of radiation or other effectors as a more sensitive predictor than testing mRNA expression. Following irradiation with X-rays, increased MRP1, MRP2, and/or P-gp protein expression was observed with increased resistance to anticancer drugs, but no P-gp mRNA increases in human or in animal models. The results of the analysis support suggestion that standard X-ray radiation might affect clinical efficacy of subsequent or concurrent chemotherapy, and that the complex effects of different types of radiation on the activity and expression of both the enzymes (*e.g.*, cytochrome P450, oxidative stress enzymes) and transporters, and shows that these effects might impact the ADME properties of drugs (8).

The collective data were also used to analyze fractions of the oxidoreductase enzymes (flavin-containing monooxygenases (FMOs), aldo-keto reductases (AKR), monoamine oxidases (MAOs), and cytochrome P450) in metabolic reactions of xenobiotic and natural chemicals. Calculations were performed by calculating the number of reactions in which a particular chemical interacted with a specific enzyme. As anticipated, the results show that 92 to 96% of metabolic oxidation-reduction reactions of all chemicals for which data were analyzed are catalyzed by P450s. FMO, AKR, and MAO enzymes collectively participate in metabolism of all chemicals to the extent of ~5%. Analysis of P450s participation in metabolism of general chemicals (environmental/industrial) revealed that the major participating P450 enzymes were 1A2 (15%), 3A4 (13%), P450 1A1 (11%), 2D6 and 2E1 (8% each), 2C9 (7 %), 2C19, and 1B1 and P450 2B6 (6% each). Minor contributions were

calculated for P450s 2A6 (5%), 2C8 (3%), and 3A5 (2%). Other P450 enzymes contributed a total of 10% to the metabolic reactions. These results are in good agreement with the results on the participation of the major enzymes in activation of potential toxicants (i.e. P450s 1A1, 1A2, 1B1, 2A6, 2E1, and 3A4) (10). With regard to participation of P450s in metabolism, analyzing the data for drugs under development and marketed drugs, showed that the major enzymes are P450s 3A4 (27%), 2D6 (13%), 2C9 (10%), 2C19 (9%), and 1A2 (9%). Minor contributions were seen for P450s 3A5 (6%), 1A1 and 2C8 (5% each), 2B6 (4%), 2E1 (3%), 2A6 (2%), and 1B1 (1%). All other human P450s contributed a total of 6% to the metabolic reactions (20). Calculations of the fractions of activation reactions of potential carcinogens attributed to group of enzymes (FMO, AKR, MAO, SULT, NAT, COX, and P450) revealed that metabolic activation of potential carcinogens are dominated by reactions catalyzed by P450 enzymes (66% of bioactivations), especially the three Family 1 P450 enzymes (1A1, 1A2, 1B1), and P450s 2A6, 2E1, and 3A4. The six enzymes collectively account for 77% of the P450 activation reaction, and Family 1 enzymes are prominent in activations of PAHs and heterocyclic amines, aryl amines and other compounds/amines. The SULT and AKR enzymes were also highly represented in activation reactions with 13% and 8%, respectively [18].

These examples illustrate that, in addition to searching the database for specific information such as substrates, inducers, inhibitors *etc.* more complex analysis can be done on xenobiotic and endobiotic metabolism which might find application pharmacology, endocrinology, toxicology, oncology, clinical application of drugs, veterinary science, and for understanding the processes in the environment.

8. CONCLUSIONS

The paper describes the development of drugs and other chemicals offline and Web-searchable metabolism databases over time and their benefits and uses. Increases in the published data in the field of xenobiotics metabolism since the year 1990 is in the present paper, exemplified by the data published on the environmental pollutant benzo[a]pyrene (B[a]P) collected up to the year 2017 (Tables 1–6). Comparison of published data on metabolism of B[a]P catalyzed by P450 enzymes using human models as presented in Table 1 (collected for the year 1990) with those presented in Table 3 (data collected up to year 2008) shows enormous data accumulation, which is difficult to follow by usual literature searches and analysis. This is followed by the addition of data on the metabolism of endo- and xenobiotics using other model species and other metabolism enzymes (*e.g.* AKRs, ADHs, CAs, CDK, CES, COX-2, EPHs, HSDH, NQO1, QR1, PDEs, PFK, SULTs, UGTs). To follow new published data, the database is updated quarterly each year. In such a way the metabolism database provides a quick and accurate approach to both new and previously published data. The information collected can be used for prediction of metabolic drug-drug (in clinics), and/or other drug-chemical interactions which might be used in clinical and environmental studies [1–4,8,9]. The collected data also contain information on drug-metabolic enzyme interactions in course of specific therapies [7,8] that might result in enhanced toxicity of a drug or affect the outcome of the therapy. Example data presented in Table 3 illustrate results on the metabolism of the environmental pollutant benzo[a]pyrene and its metabolites by the P450 1 Family of enzymes and variants. In this example, the data

included indicate also toxicological properties of the products of specific reactions. In addition, the data provide information on how the compound searched, or its metabolite, acts as an inducer or inhibitor of the metabolic reaction(s), and in such a way have additional effects on the toxicological/pharmacological outcome of therapy. In conclusion, the offline and Web-searchable database developed during past 27-years had wide range of applications (e.g. computer assisted drug design and development, optimization of clinical therapy, toxicological applications) as well as when adjustment in everyday life styles such as preparing daily meals to support particular therapies.

ABBREVIATIONS

ADME

absorption, distribution, metabolism, and excretion

NO synthase

nitric oxide synthase

PAHs

polycyclic aromatic hydrocarbons

P-gp

P-glycoprotein

MRP

multidrug resistance-associated protein

UDP

uridine diphosphate

(+)-anti-diol-B[a]P-epoxide

(+)-benzo[a]pyrene-7,8-dihydrodiol-9,10-epoxide

AhR agonist

aryl hydrocarbon receptor

Cdh

(-)-carveol dehydrogenase

CDK

cyclin-dependent kinase

AKR

aldo-keto reductase

EPHs

EHs, epoxide hydrolase

COX-2

cyclooxygenase-2

HSDH

hydroxysteroid dehydrogenase

NQO1

NAD(P)H-quinone oxidoreductase 1

QR1

quinone reductase type 1

NAT*N*-acetyltransferase**PhIP**2-amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine**PCBs**

polychlorinated biphenyls

LRP

lung resistance-related protein

BCRP1

breast cancer resistance protein 1

HSDs

hydroxysteroid dehydrogenases

PDEs

phosphodiesterases

PFK

phosphofructokinase

ADHs

alcohol dehydrogenases

CAs

carbonic anhydrases

CES

carboxylesterase

UGTs

UDP-glucuronosyltransferases

SULTs

sulfotransferases

References

1. Rendic S, Di Carlo F. Human cytochrome P450 enzymes: a status report summarizing their reactions, substrates, inducers and inhibitors. *Drug Metab. Rev.* 1997; 29(1–2):413–580. [PubMed: 9187528]
2. Rendic S. Summary of information on human CYP enzymes: human P450 metabolism data. *Drug Metab. Rev.* 2002; 34(1–2):83–448. [PubMed: 11996015]
3. Guengerich FP. Update information on human P450s. *Drug Metab. Rev.* 2002; 34(1–2):7–15. [PubMed: 11996014]
4. Guengerich FP, Rendic S. Update information on drug metabolism systems-- 2009, Part I. *Curr. Drug Metab.* 2010; 11(1):1–3. [PubMed: 20307256]
5. Kim RB. Drugs as P-glycoprotein substrates, inhibitors, and inducers. *Drug Metab. Rev.* 2002; 34(1–2):47–54. [PubMed: 11996011]
6. Gradhand U, Kim RB. Pharmacogenomics of MRP transporters (ABCC1–5) and BCRP (ABCG2). *Drug Metab. Rev.* 1998; 40(2):317–54.
7. Rendic S, Guengerich FP. Update information on drug metabolism systems-- 2009, Part II. Summary of information on the effects of diseases and environmental factors on human cytochrome P450 (CYP) enzymes and transporters. *Curr. Drug Metab.* 2010; 11(1):4–84. [PubMed: 20302566]
8. Rendic S, Guengerich FP. Summary of information on the effects of ionizing and non-ionizing irradiation on cytochrome P450 and other drug metabolizing enzymes and transporters. *Curr. Drug Metab.* 2012; 13(6):787–814. [PubMed: 22571481]
9. Guengerich FP, Shimada T. Oxidation of toxic and carcinogenic chemicals by human cytochrome P-450 enzymes. *Chem. Res. Toxicol.* 1991; 4(4):391–407. [PubMed: 1912325]
10. Shimada T, Guengerich FP. Evidence for cytochrome P-450_{NF}, the nifedipine oxidase, being the principal enzyme involved in the bioactivation of aflatoxins in human liver. *Proc. Natl. Acad. Sci. U. S. A.* 1989; 86(2):462–465. [PubMed: 2492107]
11. Shimada T, Iwasaki M, Martin MV, Guengerich FP. Human liver microsomal cytochrome P-450 enzymes involved in the bioactivation of procarcinogens detected by umu gene response in *Salmonella typhimurium* TA1535/pSK1002. *Cancer Res.* 1989; 49(12):3218–3228. [PubMed: 2655891]
12. Shimada T, Martin MV, Pruess-Schwartz D, Marnett LJ, Guengerich FP. Roles of individual human cytochrome P450 enzymes in the bioactivation of benzo[a]pyrene, 7,8-dihydroxy-7,8-dihydrobenzo[a]pyrene, and other dihydrodiol derivatives of polycyclic aromatic hydrocarbons. *Cancer Res.* 1989; 49(22):6304–6312. [PubMed: 2509067]
13. Thier R, Pemble SE, Taylor JB, Humphreys WG, Persmark M, Ketterer B, Guengerich FP. Expression of mammalian glutathione S-transferase 5–5 in *Salmonella typhimurium* TA1535 leads to base-pair mutations upon exposure to dihalomethanes. *Proc. Natl. Acad. Sci. U. S. A.* 1993; 90(18):8576–8580. (1993). [PubMed: 8378332]
14. Glatt H, Bartsch I, Christoph S, Coughtrie MWH, Falany CN, Hagen M, Landsiedel R, Pabel U, Phillips DH, Seidel A, Yamazoe Y. Sulfotransferase-mediated activation of mutagens studied using heterologous expression systems. *Chem.-Biol. Interact.* 1998; 109(1–3):195–219. [PubMed: 9566746]
15. Kellerman G, Luyten-Kellerman M, Shaw CR. Genetic variation of aryl hydrocarbon hydroxylase in human lymphocytes. *Am. J. Human Genet.* 1973; 25:327–331. [PubMed: 4704864]
16. Kellerman G, Shaw CR, Luyten-Kellerman M. Aryl hydrocarbon hydroxylase inducibility and bronchogenic carcinoma. *New Engl. J. Med.* 1973; 298:934–937.
17. Butler MA, Lang NP, Young JF, Caporaso NE, Vineis P, Hayes RB, Teitel CH, Massengill JP, Lawsen MF, Kadlubar FF. Determination of CYP1A2 and NAT2 phenotypes in human populations by analysis of caffeine urinary metabolites. *Pharmacogenetics.* 1992; 2(3):116–127. [PubMed: 1306111]
18. Rendic S, Guengerich FP. Contributions of human enzymes in carcinogen metabolism. *Chem. Res. Toxicol.* 2012; 25(7):1316–1383. [PubMed: 22531028]
19. ADME Database. Fujitsu Kyushu System Ltd.; Fukuoka, Japan: <http://jp.fujitsu.com/group/kyushu/en/services/admedatabase/> [Accessed October 27th, 2017]

20. Rendic S, Guengerich FP. Survey of human oxidoreductases and cytochrome P450 enzymes involved in the metabolism of xenobiotic and natural. *Chem. Res. Toxicol.* 2015; 28(1):38–42. [PubMed: 25485457]
21. Ruan Q, Gelhaus SL, Penning TM, Harvey RG, Blair IA. Aldo-keto reductase- and cytochrome P450-dependent formation of benzo[*a*]pyrene-derived DNA adducts in human bronchoalveolar cells. *Chem. Res. Toxicol.* 2007; 20(3):424–431. [PubMed: 17295519]
22. Jiang H, Shen YM, Quinn AM, Penning TM. Competing roles of cytochrome P450 1A1/1B1 and aldo-keto reductase 1A1 in the metabolic activation of (±)-7,8-dihydroxy-7,8-dihydrobenzo[*a*]pyrene in human bronchoalveolar cell extracts. *Chem. Res. Toxicol.* 2005; 18(2):365–374. [PubMed: 15720144]
23. Penning TM. Human aldo-keto reductases and the metabolic activation of polycyclic aromatic hydrocarbons. *Chem. Res. Toxicol.* 2014; 27(11):1901–17. [PubMed: 25279998]
24. Smith JN, Mehinagic D, Nag S, Crowell SR, Corley RA. *In vitro* metabolism of benzo[*a*]pyrene-7,8-dihydrodiol and dibenzo[*def,p*]chrysene-11,12 diol in rodent and human hepatic microsomes. *Toxicol. Lett.* 2017; 269:23–32. [PubMed: 28119020]
25. Shimada T, Murayama N, Yamazaki H, Tanaka K, Takenaka S, Komori M, Kim D, Guengerich FP. Metabolic activation of polycyclic aromatic hydrocarbons and aryl and heterocyclic amines by human cytochromes P450 2A13 and 2A6. *Chem. Res. Toxicol.* 2013; 26(4):529–37. [PubMed: 23432465]
26. Shimada T, Gillam E, Oda Y, Tsumura F, Sutter TR, Guengerich FP, Inoue K. Metabolism of Benzo[*a*]pyrene to trans-7,8-dihydroxy-7,8-dihydrobenzo[*a*]pyrene by recombinant human cytochrome P450 1B1 and purified liver epoxide hydrolase. *Chem. Res. Toxicol.* 1999; 12(7):623–9. [PubMed: 10409402]
27. Shimada T, Hayes CL, Yamazaki H, Amin S, Hecht SS, Guengerich FP, Sutter TR. Activation of chemically diverse procarcinogens by human cytochrome P450 1B1. *Cancer Res.* 1996; 56(13):2979–2984. [PubMed: 8674051]
28. Shimada T. Xenobiotic-metabolizing enzymes involved in activation and detoxification of carcinogenic polycyclic aromatic hydrocarbons. *Drug Metab Pharmacokinet.* 2006; 21(4):257–276. [PubMed: 16946553]
29. Shimada T. Inhibition of carcinogen-activating cytochrome P450 enzymes by xenobiotic chemicals in relation to antimutagenicity and anticarcinogenicity. *Toxicol. Res.* 2017; 33(2):79–96. [PubMed: 28443179]
30. Šulc M, Indra R, Moserová M, Schmeiser HH, Frei E, Arlt VM, Stiborová M. The impact of individual cytochrome P450 enzymes on oxidative metabolism of benzo[*a*]pyrene in human livers. *Environ. Mol. Mutagen.* 2016; 57(3):229–35. [PubMed: 26919089]
31. Shiizaki K, Kawanishi M, Yagi T. Modulation of benzo[*a*]pyrene-DNA adduct formation by CYP1 inducer and inhibitor. *Genes Environ.* 2017; 39:14. [PubMed: 28405246]
32. Moorthy B, Chu C, Carlin DJ. Polycyclic aromatic hydrocarbons: from metabolism to lung cancer. *Toxicol. Sci.* 2015; 145(1):5–15. [PubMed: 25911656]
33. Konstandi M, Johnson EO, Lang MA. Consequences of psychophysiological stress on cytochrome P450-catalyzed drug metabolism. *Neurosci. Biobehav. Rev.* 2014; 45:149–167. **Legends to the Tables:** [PubMed: 24877684]
34. Shou M, Gonzalez FJ, Gelboin HV. Stereoselective epoxidation and hydration at the K-region of polycyclic aromatic hydrocarbons by cDNA-expressed cytochromes P450 1A1, 1A2, and epoxide hydrolase. *Biochemistry.* 1996; 35(49):15807–15813. [PubMed: 8961944]
35. Uppstad H, Øvrebø S, Haugen A, Møllerup S. Importance of CYP1A1 and CYP1B1 in bioactivation of benzo[*a*]pyrene in human lung cell lines. *Toxicol. Lett.* 2010; 192(2):221–228. [PubMed: 19879933]
36. Jiang H, Gelhaus SL, Mangal D, Harvey GR, Blair IA, Quinn AM, Penning TM. Metabolism of benzo[*a*]pyrene in human bronchoalveolar H358 cells using liquid chromatography–mass spectrometry. *Chem. Res. Toxicol.* 2007; 20(9):1331–1341. [PubMed: 17702526]
37. Quinn AM, Penning TM. Comparisons of (+/–)-benzo[*a*]pyrene-*trans*-7,8-dihydrodiol activation by human cytochrome P450 and aldo-keto reductase enzymes: effect of redox state and expression levels. *Chem. Res. Toxicol.* 2008; 21(5):1086–1094. [PubMed: 18402469]

1. Nebert DW, Nelson DR, Adesnik M, Coon MJ, Estabrook RW, Gonzalez FJ, Guengerich FP, Gunsalus IC, Johnson EF, Kemper B, Levin W, Phillips IR, Sato R, Waterman MR. The P450 superfamily: updated listing of all genes and recommended nomenclature for the chromosomal loci. *DNA*. 1989; 8(1):1–13. [PubMed: 2651058]
2. Ioannides C, Parke DV. The cytochrome P450 I gene family of microsomal hemoproteins and their role in the metabolic activation of chemicals. *Drug Metab. Rev.* 1990; 22(1):1–85. [PubMed: 2199176]
3. Shimada T, Iwasaki M, Martin MV, Guengerich FP. Human liver microsomal cytochrome P-450 enzymes involved in the bioactivation of procarcinogens detected by umu gene response in *Salmonella typhimurium* TA1535/pSK1002. *Cancer Res.* 1989; 49(12):3218–3228. [PubMed: 2655891]
4. Wallin H, Mikalsen A, Guengerich FP, Ingelman-Sundberg M, Solberg KE, Rossland OJ, Alexander J. Differential rates of metabolic activation and detoxication of the food mutagen 2-amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine by different cytochrome P450 enzymes. *Carcinogenesis*. 1990; 11(3):489–492. [PubMed: 2311193]
5. Matsunaga T, Nomoto M, Kozak CA, Gonzalez FJ. Structure and *in vitro* transcription of the rat CYP2A1 and CYP2A2 genes and regional localization of the CYP2A gene subfamily on mouse chromosome 7. *Biochemistry*. 1989; 29(5):1329–1341.
6. Aoyama T, Korzekwa K, Nagata K, Adesnik M, Reiss A, Lapenson DP, Gillette J, Gelboin HV, Waxman DJ, Gonzalez FJ. Sequence requirements for cytochrome P-450IIB1 catalytic activity. Alteration of the stereospecificity and regioselectivity of steroid hydroxylation by a simultaneous change of two hydrophobic amino acid residues to phenylalanine. *J. Biol. Chem.* 1989; 264(35): 21327–21333. [PubMed: 2574176]
7. Park SS, Waxman DJ, Lapenson DP, Schenkman JB, Gelboin HV. Monoclonal antibodies to rat liver cytochrome P-450 2c/RLM5 that regiospecifically inhibit steroid metabolism. *Biochem. Pharmacol.* 1989; 38(18):3067–3074. [PubMed: 2783161]
8. Todorovic R, Devanesan PD, Cavalieri EL, Rogan EG, Park SS, Gelboin HV. A monoclonal antibody to rat liver cytochrome P450 IIC11 strongly and regiospecifically inhibits constitutive benzo[a]pyrene metabolism and DNA binding. *Mol. Carcinog.* 1991; 4(4):308–314. [PubMed: 1872951]
9. Matsunaga E, Zeugin T, Zanger UM, Aoyama T, Meyer UA, Gonzalez FJ. Sequence requirements for cytochrome P-450IID1 catalytic activity. A single amino acid change (Ile380 Phe) specifically decreases V_{max} of the enzyme for bufuralol but not debrisoquine hydroxylation. *J. Biol. Chem.* 1990; 265(28):17197–17201. [PubMed: 1976628]
10. Matsunaga E, Zanger UM, Hardwick JP, Gelboin HV, Meyer UA, Gonzalez FJ. The CYP2D gene subfamily: analysis of the molecular basis of the debrisoquine 4-hydroxylase deficiency in DA rats. *Biochemistry*. 1989; 28(18):7349–7355. [PubMed: 2819073]
11. Kagimoto M, Heim M, Kagimoto K, Zeugin T, Meyer UA. Multiple mutations of the human cytochrome P450IID6 gene (CYP2D6) in poor metabolizers of debrisoquine. Study of the functional significance of individual mutations by expression of chimeric genes. *J. Biol. Chem.* 1990; 265(28):17209–17214. [PubMed: 2211621]
12. Gonzalez FJ, Gelboin HV. Transcriptional and posttranscriptional regulation of CYP2E1, an N-nitrosodimethylamine demethylase. *Princess Takamatsu Symp.* 1990; 21:157–164. [PubMed: 2134674]
13. Nhamburo PT, Kimura S, McBride OW, Kozak CA, Gelboin HV, Gonzalez FJ. The human CYP2F gene subfamily: identification of a cDNA encoding a new cytochrome P450, cDNA-directed expression, and chromosome mapping. *Biochemistry*. 1990; 29(23):5491–5499. [PubMed: 1974816]
14. Thornton-Manning JR, Ruangyuttikarn W, Gonzalez FJ, Yost GS. Metabolic activation of the pneumotoxin, 3-methylindole, by vaccinia-expressed cytochrome P450s. *Biochem. Biophys. Res. Commun.* 1991; 181(1):100–107. [PubMed: 1958177]
15. Aoyama T, Yamano S, Waxman DJ, Lapenson DP, Meyer UA, Fischer V, Tyndale R, Inaba T, Kalow W, Gelboin HV, Gonzalez FJ. Cytochrome P-450 hPCN3, a novel cytochrome P-450 IIIA gene product that is differentially expressed in adult human liver. cDNA and deduced amino acid sequence and distinct specificities of cDNA-expressed hPCN1 and hPCN3 for the metabolism of

steroid hormones and cyclosporine. *J Biol Chem.* 1989; 264(18):10388–10395. [PubMed: 2732228]

16. Larrey D, Tine M, Lettéron P, Maurel P, Loeper J, Belghiti J, Pessayre D. Metabolic activation of the new tricyclic antidepressant tianeptine by human liver cytochrome P450. *Biochem. Pharmacol.* 1990; 40(3):545–550. [PubMed: 2383287]
17. Brian WR, Sari MA, Iwasaki M, Shimada T, Kaminsky LS, Guengerich FP. Catalytic activities of human liver cytochrome P-450 IIIA4 expressed in *Saccharomyces cerevisiae*. *Biochemistry.* 1990; 29(51):11280–11292. [PubMed: 2271712]
18. Shimada T, Martin MV, Pruess-Schwartz D, Marnett L, Guengerich FP. Roles of individual human cytochrome P450 enzymes in the bioactivation of benzo[*a*]pyrene, 7,8-dihydroxy-7,8-dihydrobenzo[*a*]pyrene, and other dihydrodiol derivatives of polycyclic aromatic hydrocarbons. *Cancer Res.* 1989; 49(22):6304–6312. [PubMed: 2509067]
19. Renaud P, Cullin C, Pompon D, Beaune P, Mansuy D. Expression of human liver cytochrome P450 IIIA4 in yeast. A functional model for the hepatic enzyme. *Eur. J. Biochem.* 1990; 194(3):889–896. [PubMed: 2269307]
20. Aoyama T, Hardwick JP, Imaoka S, Funae Y, Gelboin HV, Gonzalez FJ. Clofibrate-inducible rat hepatic P450s IVA1 and IVA3 catalyze the omega- and [*omega*-1]-hydroxylation of fatty acids and the omega-hydroxylation of prostaglandins E1 and F2 *alpha*. *J. Lipid Res.* 1990; 31(8):1477–1482. [PubMed: 2280187]
21. Kimura S, Hanioka N, Matsunaga E, Gonzalez FJ. The rat clofibrate-inducible CYP4A gene subfamily. I. Complete intron and exon sequence of the CYP4A1 and CYP4A2 genes, unique exon organization, and identification of a conserved 19-bp upstream element. *DNA.* 1989; 8(7):503–516. [PubMed: 2766932]
22. Hecker M, Ullrich V. On the mechanism of prostacyclin and thromboxane A2 biosynthesis. *J. Biol. Chem.* 1989; 264(1):141–150. [PubMed: 2491846]
23. Schwarz D, Kisselev P, Honeck H, Cascorbi I, Schunck WH, Roots I. Co-expression of human cytochrome P4501A1 (CYP1A1) variants and human NADPH-cytochrome P450 reductase in the baculovirus/insect cell system. *Xenobiotica.* 2001; 31(6):345–356. [PubMed: 11513247]
24. Guo Z, Gillam EM, Ohmori S, Tukey RH, Guengerich FP. Expression of modified human cytochrome P450 1A1 in *Escherichia coli*: effects of 5' substitution, stabilization, purification, spectral characterization, and catalytic properties. *Arch Biochem Biophys.* 1994; 312(2):436–446. [PubMed: 8037457]
25. Kim JH, Stansbury KH, Walker NJ, Trush MA, Strickland PT, Sutter TR. Metabolism of benzo[*a*]pyrene and benzo[*a*]pyrene-7,8-diol by human cytochrome P450 1B1. *Carcinogenesis.* 1998; 19(10):1847–1853. [PubMed: 9806168]
26. Shimada T, Hayes CL, Yamazaki H, Amin S, Hecht SS, Guengerich FP, Sutter TR. Activation of chemically diverse procarcinogens by human cytochrome P450 1B1. *Cancer Res.* 1996; 56(13):2979–2984. [PubMed: 8674051]
27. Shimada T, Gillam EM, Sandhu P, Guo Z, Tukey RH, Guengerich FP. Activation of procarcinogens by human cytochrome P450 enzymes expressed in *Escherichia coli*. Simplified bacterial systems for genotoxicity assays. *Carcinogenesis.* 1994; 15(11):2523–9. [PubMed: 7955101]
28. Murray GI, Taylor MC, McFadyen MC, McKay JA, Greenlee WF, Burke MD, Melvin WT. Tumor-specific expression of cytochrome P450 CYP1B1. *Cancer Res.* 1997; 57(14):3026–3031. [PubMed: 9230218]
29. Shimada T, Wunsch RM, Hanna IH, Sutter TR, Guengerich FP, Gillam EM. Recombinant human cytochrome P450 1B1 expression in *Escherichia coli*. *Arch. Biochem. Biophys.* 1998; 357(1):111–120. [PubMed: 9721189]
30. Shimada T, Oda Y, Gillam EM, Guengerich FP, Inoue K. Metabolic Activation of Polycyclic Aromatic Hydrocarbons and Other Procarcinogens by Cytochromes P450 1A1 and P450 1B1 Allelic Variants and Other Human Cytochromes P450 in *Salmonella typhimurium* NM2009. *Drug. Metab. Dispos.* 2001; 29(9):1176–82. [PubMed: 11502724]
31. Buters J, Quintanilla-Martinez L, Schober W, Soballa VJ, Hintermair J, Wolff T, Gonzalez FJ, Greim H. CYP1B1 determines susceptibility to low doses of 7,12-dimethylbenz[*a*]anthracene-

- induced ovarian cancers in mice: correlation of CYP1B1-mediated DNA adducts with carcinogenicity. *Carcinogenesis*. 2003; 24(2):327–334. [PubMed: 12584184]
32. Shou M, Gonzalez FJ, Gelboin HV. Stereoselective epoxidation and hydration at the K-region of polycyclic aromatic hydrocarbons by cDNA-expressed cytochromes P450 1A1, 1A2, and epoxide hydrolases. *Biochemistry*. 1996; 35(49):15807–13. [PubMed: 8961944]
33. Shimada T, Gillam EM, Sutter TR, Strickland PT, Guengerich FP, Yamazaki H. Oxidation of xenobiotics by recombinant human cytochrome P450 1B1. *Drug. Metab. Dispos.* 1997; 25(5):617–622. [PubMed: 9152602]
34. Shimada T. Human Cytochrome P450 1B1 and chemical carcinogenesis. *Rev. Toxicol.* 1999/2000; 3:139–166.
35. Turesky RJ, Constable A, Richoz J, Varga N, Markovic J, Martin MV, Guengerich FP. Activation of heterocyclic aromatic amines by rat and human liver microsomes and by purified rat and human cytochrome P450 1A2. *Chem. Res. Toxicol.* 1998; 11(8):925–936. [PubMed: 9705755]
36. Edwards RJ, Murray BP, Murray S, Schulz T, Neubert D, Gant TW, Thorgeirsson SS, Boobis AR, Davies DS. Contribution of CYP1A1 and CYP1A2 to the activation of heterocyclic amines in monkeys and human. *Carcinogenesis*. 1994; 15(5):829–836. [PubMed: 8200083]
37. Turesky RJ, Constable A, Fay LB, Guengerich FP. Interspecies differences between rat and human P450 1A2 in the metabolism of heterocyclic aromatic amines. *Cancer Lett.* 1999; 143(2):109–112. [PubMed: 10503887]
38. Guengerich FP, Parikh A, Turesky RJ, Josephy PD. Inter-individual differences in the metabolism of environmental toxicants: cytochrome P450 1A2 as a prototype. *Mutat. Res.* 1999; 428(1–2): 115–124. [PubMed: 10517985]
39. Williams JA, Martin FL, Muir GH, Hewer A, Grover PL, Phillips DH. Metabolic activation of carcinogens and expression of various cytochromes P450 in human prostate tissue. *Carcinogenesis*. 2000; 21(9):1683–1689. [PubMed: 10964100]
40. Oda Y, Aryal P, Terashita T, Gillam EM, Guengerich FP, Shimada T. Metabolic activation of heterocyclic amines and other procarcinogens in *Salmonella typhimurium* umu tester strains expressing human cytochrome P4501A1.; 1A2.; 1B1.; 2C9.; 2D6.; 2E1.; and 3A4 and human NADPH-P450 reductase and bacterial O-acetyltransferase. *Mutat. Res.* 2001; 492(1–2):81–90. [PubMed: 11377247]
41. Aryal P, Terashita T, Guengerich FP, Shimada T, Oda Y. Use of genetically engineered *Salmonella typhimurium* OY1002/1A2 strain coexpressing human cytochrome P450 1A2 and NADPH-cytochrome P450 reductase and bacterial O-acetyltransferase in SOS/umu assay. *Environ. Mol. Mutagen.* 2000; 36(2):121–6. [PubMed: 11013410]
42. Josephy PD, Battx SM, Boverhof DR. Recombinant human P450 forms 1A1, 1A2, and 1B1 catalyze the bioactivation of heterocyclic amine mutagens in *Escherichia coli lacZ* strains. *Environ. Mol. Mutagen.* 2001; 38(1):12–8. [PubMed: 11473383]
43. Shimada T, Watanabe J, Kawajiri K, Sutter TR, Guengerich FP, Gillam EM, Inoue K. Catalytic properties of polymorphic human cytochrome P450 1B1 variants. *Carcinogenesis*. 1999; 20(8): 1607–1614. [PubMed: 10426814]
44. Watanabe J, Shimada T, Gillam EM, Ikuta T, Suemasu K, Higashi Y, Gotoh O, Kawajiri K. Association of CYP1B1 genetic polymorphism with incidence to breast and lung cancer. *Pharmacogenetics*. 2000; 10(1):25–33. [PubMed: 10739169]
45. Shimada T, Watanabe J, Inoue K, Guengerich FP, Gillam EM. Specificity of 17 β -oestradiol and benzo[*a*]pyrene oxidation by polymorphic human cytochrome P4501B1 variants substituted at residues 48, 119 and 432. *Xenobiotica*. 2001; 31(3):163–176. [PubMed: 11465393]
46. Yamazaki Y, Fujita K, Nakayama K, Suzuki A, Nakamura K, Yamazaki H, Kamataki T. Establishment of ten strains of genetically engineered *Salmonella typhimurium* TA1538 each co-expressing a form of human cytochrome P450 with NADPH-cytochrome P450 reductase sensitive to various promutagens. *Mutat. Res.* 2004; 562(1–2):151–162. [PubMed: 15279838]
47. Zhang ZY, Pelletier RD, Wong YN, Sugawara M, Zhao N, Littlefield BA. Preferential inducibility of CYP1A1 and CYP1A2 by TCDD: differential regulation in primary human hepatocytes versus transformed human cells. *Biochem. Biophys. Res. Commun.* 2006; 341(2):399–407. [PubMed: 16426572]

48. Kushman ME, Kabler SL, Fleming MH, Ravoori S, Gupta TC, Doehmer J, Morrow CS, Townsend AJ. Expression of human glutathione S-transferase P1 confers resistance to benzo[*a*]pyrene or benzo[*a*]pyrene-7,8-dihydrodiol mutagenesis, macromolecular alkylation and formation of stable N2-Gua-BPDE adducts in stably transfected V79MZ cells co-expressing hCYP1A1. *Carcinogenesis*. 2007; 28(1):207–214. [PubMed: 16885195]
49. Kim JY, Chung JY, Park JE, Lee SG, Kim YJ, Cha MS, Han MS, Lee HJ, Yoo YH, Kim JM. Benzo[*a*]pyrene induces apoptosis in RL95-2 human endometrial cancer cells by cytochrome P450 1A1 activation. *Endocrinology*. 2007; 148(10):5112–5122. [PubMed: 17640999]
50. Kushman ME, Kabler SL, Ahmad S, Doehmer J, Morrow CS, Townsend AJ. Protective efficacy of hGSTM1-1 against B[*a*]P and (+)- or (–)-B[*a*]P-7,8-dihydrodiol cytotoxicity, mutagenicity, and macromolecular adducts in V79 cells coexpressing hCYP1A1. *Toxicol. Sci.* 2007; 99(1):51–57. [PubMed: 17525473]
51. Shimada T, Gillam EM, Oda Y, Tsumura F, Sutter TR, Guengerich FP, Inoue K. Metabolism of Benzo[*a*]pyrene to trans-7,8-dihydroxy-7,8-dihydrobenzo[*a*]pyrene by recombinant human cytochrome P450 1B1 and purified liver epoxide hydrolase. *Chem. Res. Toxicol.* 1999; 12(7):623–629. [PubMed: 10409402]
52. Jones JP, Shou M, Korzekwa KR. Stereospecific activation of the procarcinogen benzo[*a*] pyrene: a probe for the active sites of the cytochrome P450 superfamily. *Biochemistry*. 1995; 34(21):6956–6961. [PubMed: 7766605]
53. Bauer E, Guo Z, Ueng YF, Bell LC, Zeldin D, Guengerich FP. Oxidation of benzo[*a*]pyrene by recombinant human cytochrome P450 enzymes. *Chem. Res. Toxicol.* 1995; 8(1):136–142. [PubMed: 7703357]
54. Gautier JC, Lecoeur S, Cosme J, Perret A, Urban P, Beaune P, Pompon D. Contribution of human cytochrome P450 to benzo[*a*]pyrene and benzo[*a*]pyrene-7,8-dihydrodiol metabolism.; as predicted from heterologous expression in yeast. *Pharmacogenetics*. 1996; 6(6):489–499. [PubMed: 9014198]
55. Shou M, Korzekwa KR, Crespi CL, Gonzalez FJ, Gelboin HV. The role of 12 cDNA-expressed human, rodent, and rabbit cytochromes P450 in the metabolism of benzo[*a*]pyrene and benzo[*a*]pyrene trans-7,8-dihydrodiol. *Mol. Carcinog.* 1994; 10(3):159–168. [PubMed: 8043197]
56. Yun CH, Shimada T, Guengerich FP. Roles of human liver cytochrome P450 2C and 3A enzymes in the 3-hydroxylation of benzo[*a*]pyrene. *Cancer Res.* 1992; 52(7):1868–1874. [PubMed: 1551116]
57. Schwarz D, Kisselev P, Cascorbi I, Schunck WH, Roots I. Differential metabolism of benzo[*a*]pyrene and benzo[*a*]pyrene-7,8-dihydrodiol by human CYP1A1 variants. *Carcinogenesis*. 2001; 22(3):453–459. [PubMed: 11238186]
58. Doehmer J, Holtkamp D, Soballa V, Raab G, Schmalix W, Seidel A, Greim H, Jacob J. Cytochrome P450 mediated reactions studied in genetically engineered V79 Chinese hamster cells. *Pharmacogenetics*. 1995; 5:91–96.
59. Schwarz D, Roots I. *In vitro* assessment of inhibition by natural polyphenols of metabolic activation of procarcinogens by human CYP1A1. *Biochem. Biophys. Res. Commun.* 2003; 303(3):902–907. [PubMed: 12670496]
60. Toriba A, Nakamura H, Chetianukornkul T, Kizu R, Makino T, Nakazawa H, Yokoi T, Hayakawa K. Method for determining monohydroxybenzo[*a*]pyrene isomers using column-switching high-performance liquid chromatography. *Anal. Biochem.* 2003; 312(1):14–22. [PubMed: 12479830]
61. Schwarz D, Kisselev P, Roots I. St. John's wort extracts and some of their constituents potentially inhibit ultimate carcinogen formation from benzo[*a*]pyrene-7,8-dihydrodiol by human CYP1A1. *Cancer Res.* 2003; 63(22):8062–8068. [PubMed: 14633740]
62. Lampen A, Ebert B, Stumkat L, Jacob J, Seidel A. Induction of gene expression of xenobiotic metabolism enzymes and ABC-transport proteins by PAH and a reconstituted PAH mixture in human *Caco-2* cells. *Biochim. Biophys. Acta.* 2004; 1681(1):38–46. [PubMed: 15566942]
63. Schmalix WA, Maser H, Kiefer F, Reen R, Wiebel FJ, Gonzalez F, Seidel A, Glatt H, Greim H, Doehmer J. Stable expression of human cytochrome P450 1A1 cDNA in V79 Chinese hamster cells and metabolic activation of benzo[*a*]pyrene. *Eur. J. Pharmacol.* 1993; 248(3):251–261. [PubMed: 8293790]

64. Jiang H, Gelhaus SL, Mangal D, Harvey RG, Blair IA, Penning TM. Metabolism of benzo[*a*]pyrene in human bronchoalveolar H358 cells using liquid chromatography-mass spectrometry. *Chem. Res. Toxicol.* 2007; 20(9):1331–1341. [PubMed: 17702526]
65. Zhang Z, Fasco MJ, Huang Z, Guengerich FP, Kaminsky LS. Human cytochromes P450 1A1 and P450 1A2: *R*-warfarin metabolism as a probe. *Drug. Metab. Dispos.* 1995; 23(12):1339–1346. [PubMed: 8689941]
66. Zhang ZY, Fasco MJ, Huang L, Guengerich FP, Kaminsky LS. Characterization of purified human recombinant cytochrome P4501A1-Ile462 and -Val462: assessment of a role for the rare allele in carcinogenesis. *Cancer Res.* 1996; 56(17):3926–2933. [PubMed: 8752159]
67. Kaminsky LS, de Morais SM, Faletto MB, Dunbar DA, Goldstein JA. Correlation of human cytochrome P450 substrate specificities with primary structure: warfarin as a probe. *Mol. Pharmacol.* 1993; 43:234–239. [PubMed: 8429826]
68. Darbyshire JF, Iyer KR, Grogan J, Korzekwa KR, Trager WF. Substrate probe for the mechanism of aromatic hydroxylation catalyzed by cytochrome P450. *Drug. Metab. Dispos.* 1996; 24:1038–1045. [PubMed: 8886617]
69. Shou M, Gonzalez FJ, Gelboin HV. Stereoselective epoxidation and hydration at the K-region of polycyclic aromatic hydrocarbons by cDNA-expressed cytochromes P450 1A1, 1A2, and epoxide hydrolases. *Biochemistry.* 1996; 35(49):15807–15813. [PubMed: 8961944]
70. Kunze, KL. ISSX Proceedings of the 4th International ISSX Meeting. Vol. 8. Seattle, WA, USA: Aug 27. Sep 27. 1995 Prediction and management of metabolism-based drug interactions, *in vitro* - *in vivo* correlations; p. 4
71. Wienkers, LC., Kunze, KL., Trager, WF. The effect of fluconazole on the metabolism of the warfarin enantiomers by human liver microsomes. ISSX Proceedings; 5th North American ISSX Meeting; Bal Harbour, Florida, USA. November, 2–6. 1992; p. 20
72. Kunze KL, Wienkers LC, Thummel KE, Trager WF. Warfarin-fluconazole I- Inhibition of the human cytochrome P450-dependent metabolism of warfarin by fluconazole: *in vitro* studies. *Drug. Metab. Dispos.* 1996; 24(4):414–421. [PubMed: 8801056]
73. Wienkers LC, Wurden CJ, Storch E, Kunze KL, Rettie AE, Trager WF. Formation of (*R*)-8-hydroxywarfarin in human liver microsomes. A new metabolic marker for the (*S*)-mephenytoin hydroxylase, P4502C19. *Drug. Metab. Dispos.* 1996; 24(5):610–614. [PubMed: 8723744]
74. Kaminsky LS, Zhang ZY. Human P450 metabolism of warfarin. *Pharmacol. Ther.* 1997; 73(1):67–74. [PubMed: 9014207]
75. Persson I, Johansson I, Ingelman-Sundberg M. *In vitro* kinetics of two human CYP1A1 variant enzymes suggested to be associated with interindividual differences in cancer susceptibility. *Biochem Biophys Res Commun.* 1997; 231(1):227–230. [PubMed: 9070254]
76. Guengerich FP. The 1992 Bernard B. Brodie Award Lecture. Bioactivation and detoxication of toxic and carcinogenic chemicals. *Drug. Metab. Dispos.* 1993; 21(1):1–6. [PubMed: 8095200]
77. Brian WR, Srivastava PK, Umbenhauer DR, Lloyd RS, Guengerich FP. Expression of a human liver cytochrome P-450 protein with tolbutamide hydroxylase activity in *Saccharomyces cerevisiae*. *Biochemistry.* 1989; 28(12):4993–4999. [PubMed: 2669966]
78. Knodell RG, Dubey RK, Wilkinson GR, Guengerich FP. Oxidative metabolism of hexobarbital in human liver: relationship to polymorphic *S*-mephenytoin 4-hydroxylation. *J. Pharmacol. Exp. Ther.* 1988; 245(3):845–849. [PubMed: 3385644]
79. Funck-Brentano C, Turgeon J, Woosley RL, Roden DM. Effect of low dose quinidine on encainide pharmacokinetics and pharmacodynamics. Influence of genetic polymorphism. *J. Pharmacol. Exp. Ther.* 1989; 249(1):134–142. [PubMed: 2496225]
80. McManus ME, Burgess WM, Veronese ME, Huggett A, Quattrochi LC, Tukey RH. Metabolism of 2-acetylaminofluorene and benzo[*a*]pyrene and activation of food-derived heterocyclic amine mutagens by human cytochromes P-450. *Cancer Res.* 1990; 50(11):3367–3376. [PubMed: 2334931]
81. Mammen JS, Kleiner HE, DiGiovanni J, Sutter TR, Strickland PT. Coumarins are competitive inhibitors of cytochrome P450 1B1, with equal potency for allelic variants. *Pharmacogenet. Genomics.* 2005; 15(3):183–188. [PubMed: 15861043]

82. Guengerich FP, Chun YJ, Kim D, Gillam EM, Shimada T. Cytochrome P450 1B1: a target for inhibition in anticarcinogenesis strategies. *Mutat. Res.* 2003; 523–524:173–82.
83. Wu ZL, Sohl CD, Shimada T, Guengerich FP. Recombinant enzymes overexpressed in bacteria show broad catalytic specificity of human cytochrome P450 2W1 and limited activity of human cytochrome P450 2S1. *Mol. Pharmacol.* 2006; 69(6):2007–2014. [PubMed: 16551781]
84. Aklillu E, Ovrebo S, Botnen IV, Otter C, Ingelman-Sundberg M. Characterization of common CYP1B1 variants with different capacity for benzo[*a*]pyrene-7,8-dihydrodiol epoxide formation from benzo[*a*]pyrene. *Cancer Res.* 2005; 65(12):5105–5111. [PubMed: 15958554]
85. Lee YS, Reidenberg MM. Grapefruit juice and its flavonoids inhibit 11 *beta*-hydroxysteroid dehydrogenase. *Clin. Pharmacol. Ther.* 1996; 59(1):62–71. [PubMed: 8549035]
86. Mancy A, Broto P, Dijols S, Dansette PM, Mansuy DA. The substrate binding site of human liver cytochrome P450 2C9: an approach using designed tienilic acid derivatives and molecular modeling. *Biochemistry.* 1995; 34(33):10365–10375. [PubMed: 7654690]
87. Drenth HJ, Bouwman CA, Seinen W, Van den Berg M. Effects of some persistent halogenated environmental contaminants on aromatase (CYP19) activity in the human choriocarcinoma cell line JEG-3. *Toxicol. Appl. Pharmacol.* 1998; 148(1):50–55. [PubMed: 9465263]
88. Letcher RJ, van Holsteijn I, Drenth HJ, Norstrom RJ, Bergman A, Safe S, Pieters R, van den Berg M. Cytotoxicity and aromatase (CYP19) activity modulation by organochlorines in human placental JEG-3 and JAR choriocarcinoma cells. *Toxicol. Appl. Pharmacol.* 1999; 160(1):10–20. [PubMed: 10502498]
89. Shimada T, Guengerich FP. Inhibition of human cytochrome P450 1A1-, 1A2-, and 1B1-mediated activation of procarcinogens to genotoxic metabolites by polycyclic aromatic hydrocarbons. *Chem. Res. Toxicol.* 2006; 19(2):288–294. [PubMed: 16485905]
90. Spink DC, Katz BH, Hussain MM, Spink BC, Wu SJ, Liu N, Pause R, Kaminsky LS. Induction of CYP1A1 and CYP1B1 in T-47D human breast cancer cells by benzo[*a*]pyrene is diminished by arsenite. *Drug. Metab. Dispos.* 2002; 30(3):262–269. [PubMed: 11854143]
91. Shimada T, Murayama N, Okada K, Funae Y, Yamazaki H, Guengerich FP. Different mechanisms for inhibition of human cytochromes P450 1A1, 1A2, and 1B1 by polycyclic aromatic inhibitors. *Chem. Res. Toxicol.* 2007; 20(3):489–496. [PubMed: 17291012]
92. Wanchana S, Yamashita F, Hashida M. QSAR analysis of the inhibition of recombinant CYP3A4 activity by structurally diverse compounds using a genetic algorithm-combined partial least squares method. *Pharm. Res.* 2003; 20(9):1401–1408. [PubMed: 14567634]
93. Morinaga H, Yanase T, Nomura M, Okabe T, Goto K, Harada N, Nawata H. A benzimidazole fungicide benomyl, and its metabolite, carbendazim, induce aromatase activity in a human ovarian granulosa-like tumor cell line (KGN). *Endocrinology.* 2004; 145(4):1860–1869. [PubMed: 14691014]
94. Chun HS, Kim HJ, Kim Y, Chang HJ. Inhibition of the benzo[*a*]pyrene-induced toxicity by allyl sulfides in human epidermal keratinocytes. *Biotechnol. Lett.* 2004; 26(22):1701–1706. [PubMed: 15604822]
95. Chun HS, Chang HJ, Choi EH, Kim HJ, Ku KH. Molecular and absorption properties of 12 soy isoflavones and their structure-activity relationship with selected biological activities. *Biotechnol. Lett.* 2005; 27(15):1105–1111. [PubMed: 16132860]
96. Guengerich, FP. Human cytochrome P450 enzymes. In: Ortiz de Montellano, PR., editor. *Cytochrome P450: Structure, Mechanism, and Biochemistry.* 2. Plenum Press; N.Y: 1995. p. 473–535.
97. Burchiel SW, Thompson TA, Lauer FT, Oprea TI. Activation of dioxin response element (DRE)-associated genes by benzo(*a*)pyrene 3.:6-quinone and benzo(*a*)pyrene 1.:6-quinone in MCF-10A human mammary epithelial cells. *Toxicol. Appl. Pharmacol.* 2007; 221(2):203–214. [PubMed: 17466351]
98. Lewis DF, Ioannides C, Parke DV. Molecular modeling of cytochrome CYP1A1: a putative access channel explains differences in induction potency between the isomers benzo[*a*]pyrene and benzo[*e*]pyrene.; and 2- and 4-acetylaminofluorene. *Toxicol. Lett.* 1994; 71(3):235–243. [PubMed: 8160212]

99. Lewis DF, Moereel sH, Lake BG, Ioannides C, Parke DV. Molecular modeling of enzymes and receptors involved in carcinogenesis. QSARs and compact-3D. *Drug Metabol. Rev.* 1994; 26(1–2): 261–285.
100. Ioannides C, Parke DV. Induction of cytochrome P4501 as an indicator of potential chemical carcinogenesis. *Drug Metabol. Rev.* 1993; 25(4):485–501.
101. Juchau MR, Lee QP, Fantel AG. Xenobiotic biotransformation/bioactivation in organogenesis-stage conceptual tissues. *Drug Metabol. Rev.* 1992; 24(2):195–238.
102. McLemore TL, Adelberg S, Liu MC, McMahon NA, Yu SJ, Hubbard WC, Czerwinski M, Wood TG, Storeng R, Lubet RA, Eggleston JC, Boyd MR, Hines RN. Expression of CYP1A1 gene in patients with lung cancer: evidence for cigarette smoke-induced gene expression in normal lung tissue and for altered gene regulation in primary pulmonary carcinomas. *J. Natl. Cancer Inst.* 1990; 82(16):1333–1339. [PubMed: 2380990]
103. Kawajiri K, Nakachi K, Imai K, Watanabe J, Hayashi S. The *CYP1A1* gene and cancer susceptibility. *Crit. Rev. Oncol. Hematol.* 1993; 14(1):77–87. [PubMed: 8103989]
104. Einolf HJ, Story WT, Marcus CB, Larsen MC, Jefcoate CR, Greenlee WF, Yagi H, Jerina DM, Amin S, Park SS, Gelboin HV, Baird WM. Role of cytochrome P450 enzyme induction in the metabolic activation of benzo[*c*]phenanthrene in human cell lines and mouse epidermis. *Chem. Res. Toxicol.* 1997; 10(5):609–617. [PubMed: 9168260]
105. Seidel A, Soballa VJ, Raab G, Frank H, Greim H, Grimmer G, Jacob J, Doehmer J. Regio- and stereoselectivity of metabolism of benzo[*c*]phenanthrene mediated by genetically engineered V79 chinese hamster cells expressing rat and human cytochromes P450. *Environ. Toxicol. Pharmacol.* 1998; 5(3):179–196. [PubMed: 21781864]
106. Baum M, Amin S, Guengerich FP, Hecht SS, Kohl W, Eisenbrand G. Metabolic Activation of benzo[*c*]phenanthrene by cytochrome P450 enzymes in human liver and lung. *Chem. Res. Toxicol.* 2001; 14(6):686–693. [PubMed: 11409939]
107. Langouet S, Furge LL, Kerriguy N, Nakamura K, Guillouzo A, Guengerich FP. Inhibition of human cytochrome P450 enzymes by 1,2-dithiole-3-thionem oltipraz and its derivatives, and sulfuraphane. *Chem. Res. Toxicol.* 2000; 13(4):245–252. [PubMed: 10775323]
108. Le Ferrec E, Lagadic-Gossman D, Rauch C, Bardiau C, Maheo K, Guillouzo A, Morel F. Abstracts from the 6th International ISSX Meeting, Munich, Germany, October 7–11. Transcriptional induction of CYP1A1 by oltipraz in human Caco-2 cells is calcium-dependent. *Drug Metab. Rev.* 2001; 33(Suppl. 1):145.
109. Sofowora GG, Choo EF, Mayo G, Shyr Y, Wilkinson GR. *In vivo* inhibition of human CYP1A2 activity by oltipraz. *Cancer. Chemother. Pharmacol.* 2001; 47(6):505–510. [PubMed: 11459203]
110. Leferrec E, Lagadic-Gossmann D, Rauch C, Bardiau C, Maheo K, Massiere F, Le Vee M, Guillouzo A, Morel F. Transcriptional induction of CYP1A1 by oltipraz in human Caco-2 cells is Ah receptor- and calcium-dependent. *J. Biol. Chem.* 2002; 277(27):24780–24788. [PubMed: 11959854]
111. Cherng SH, Lin P, Yang JL, Hsu SL, Lee H. Benzo[*g,h,i*]perylene synergistically transactivates benzo[*a*]pyrene-induced *cyp1a1* gene expression by aryl hydrocarbon receptor pathway. *Toxicol. Appl. Pharmacol.* 2001; 170(1):63–68. [PubMed: 11141357]
112. Iba MM, Wei C, Weyand EH, Chen S, Caccavale RJ. Abstracts from the 6th International ISSX Meeting, Munich, Germany, October 7–11, 2001. Inducibility of CYP1A expression in cultured human lung explants. *Drug Metab Rev.* 7–11. 2001; 33(Suppl. 1):143.
113. Iwanari M, Nakajima M, Kizu R, Hayakawa K, Yokoi T. Induction of CYP1A1, CYP1A2, and CYP1B1 mRNAs by nitropolycyclic aromatic hydrocarbons in various human tissue-derived cells, chemical-, cytochrome P450 isoform-, and cell-specific differences. *Arch. Toxicol.* 2002; 76(5–6):287–298. [PubMed: 12107646]
114. Cavin C, Bezencon C, Guignard G, Schilter B. Coffee diterpenes prevent benzo[*a*]pyrene genotoxicity in rat and human culture systems. *Biochem. Biophys. Res. Commun.* 2003; 306(2): 488–95. [PubMed: 12804590]
115. Baird WM, Mahadevan B, Marston CP, Courter LA. Abstracts from the 7th International ISSX Meeting, Vancouver, Canada, August 29–September, 2004. Effect of environmental mixtures

containing polycyclic aromatic hydrocarbons on cytochrome P450 levels in mouse epidermis and human cells in culture. *Drug. Metab. Rev.* 2004; 36(Suppl. 1):123.

116. Mahadevan B, Parsons H, Musafia T, Sharma AK, Amin S, Pereira C, Baird WM. Effect of artificial mixtures of environmental polycyclic aromatic hydrocarbons present in coal tar, urban dust, and diesel exhaust particulates on MCF-7 cells in culture. *Environ. Mol. Mutagen.* 2004; 44(2):99–107. [PubMed: 15278913]
117. Lemm F, Wilhelm M, Roos PH. Occupational exposure to polycyclic aromatic hydrocarbons suppresses constitutive expression of CYP1B1 on the transcript level in human leukocytes. *Int. J. Hyg. Environ. Health.* 2004; 207(4):325–335. [PubMed: 15471096]
118. Mahadevan B, Marston CP, Dashwood WM, Li Y, Pereira C, Baird WM. Effect of a standardized complex mixture derived from coal tar on the metabolic activation of carcinogenic polycyclic aromatic hydrocarbons in human cells in culture. *Chem. Res. Toxicol.* 2005; 18(2):224–231. [PubMed: 15720126]
119. Bonvallot V, Baeza-Squiban A, Baulig A, Brulant S, Boland S, Muzeau F, Barouki R, Marano F. Organic compounds from diesel exhaust particles elicit a proinflammatory response in human airway epithelial cells and induce cytochrome p450 1A1 expression. *Am. J. Respir. Cell Mol. Biol.* 2001; 25(4):515–521. [PubMed: 11694458]
120. Mahadevan B, Keshava C, Musafia-Jeknic T, Pecaj A, Weston A, Baird WM. Altered gene expression patterns in MCF-7 cells induced by the urban dust particulate complex mixture standard reference material 1649a. *Cancer Res.* 2005; 65(4):1251–1258. [PubMed: 15735009]
121. Cheung Y, Ferrari MP, Cooke BR, Cybulski ZR, Anacardio R, Novellini R, Colotta F, Hall M. Abstracts from the 7th International ISSX Meeting, Vancouver, Canada, August 29–September 3, 2004. Identification of the cytochromes P450 responsible for the human hepatic metabolism of repertaxin. *Drug Metab. Rev.* 2004; 36(Suppl. 1):70.
122. Hooven LA, Mahadevan B, Keshava C, Johns C, Pereira C, Desai D, Amin S, Weston A, Baird WM. Effects of suberoylanilide hydroxamic acid and trichostatin A on induction of cytochrome P450 enzymes and benzo[a]pyrene DNA adduct formation in human cells. *Bioorg. Med. Chem. Lett.* 2005; 15(5):1283–1287. [PubMed: 15713371]
123. Vakharia DD, Liu N, Pause R, Fasco M, Bessette E, Zhang QY, Kaminsky LS. Polycyclic aromatic hydrocarbon/metal mixtures: effect on PAH induction of CYP1A1 in human HEPG2 cells. *Drug. Metab. Dispos.* 2001; 29(7):999–1006. [PubMed: 11408366]
124. Vakharia DD, Liu N, Pause R, Fasco M, Bessette E, Zhang QY, Kaminsky LS. Effect of metals on polycyclic aromatic hydrocarbon induction of CYP1A1 and CYP1A2 in human hepatocyte cultures. *Toxicol. Appl. Pharmacol.* 2001; 170(2):93–103. [PubMed: 11162773]
125. Keshava C, Divi RL, Whipkey DL, Frye BL, McCanlies E, Kuo M, Poirier MC, Weston A. Induction of CYP1A1 and CYP1B1 and formation of carcinogen-DNA adducts in normal human mammary epithelial cells treated with benzo[a]pyrene. *Cancer Lett.* 2005; 221(2):213–224. [PubMed: 15808407]
126. Wen X, Walle UK, Walle T. 5,7-Dimethoxyflavone downregulates CYP1A1 expression and benzo[a]pyrene-induced DNA binding in Hep G2 cells. *Carcinogenesis.* 2005; 26(4):803–809. [PubMed: 15661813]
127. Wu SJ, Spink DC, Spink BC, Kaminsky LS. Quantitation of CYP1A1 and 1B1 mRNA in polycyclic aromatic hydrocarbon-treated human T-47D and HepG2 cells by a modified bDNA assay using fluorescence detection. *Anal. Biochem.* 2003; 312(2):162–166. [PubMed: 12531201]
128. Chang H, Chang LW, Cheng YH, Tsai WT, Tsai MX, Lin P. Preferential induction of CYP1A1 and CYP1B1 in CCSP-positive cells. *Toxicol. Sci.* 2006; 89(1):205–213. [PubMed: 16237193]
129. Musafia-Jeknic T, Mahadevan B, Pereira C, Baird WM. Long-term effects of a standardized complex mixture of urban dust particulate on the metabolic activation of carcinogenic polycyclic aromatic hydrocarbons in human cells in culture. *Toxicol. Sci.* 2005; 88(2):358–366. [PubMed: 16162842]
130. Cherng SH, Hsu SL, Yang JL, Yu CT, Lee H. Suppressive effect of 1-nitropyrene on benzo[a]pyrene-induced CYP1A1 protein expression in HepG2 cells. *Toxicol. Lett.* 2006; 161(3):236–243. [PubMed: 16280210]

131. Tsuji PA, Walle T. Inhibition of benzo[*a*]pyrene-activating enzymes and DNA binding in human bronchial epithelial BEAS-2B cells by methoxylated flavonoids. *Carcinogenesis*. 2006; 27(8): 1579–1585. [PubMed: 16484233]
132. Wen X, Walle T. Preferential induction of CYP1B1 by benzo[*a*]pyrene in human oral epithelial cells: impact on DNA adduct formation and prevention by polyphenols. *Carcinogenesis*. 2005; 26(10):1774–1781. [PubMed: 15905203]
133. Walle T, Walle UK, Sedmera D, Klausner M. Benzo[*a*]pyrene-induced oral carcinogenesis and chemoprevention: studies in bioengineered human tissue. *Drug. Metab. Dispos.* 2006; 34(3):346–350. [PubMed: 16381670]
134. Wen X, Walle T. Cytochrome P450 1B1.; a novel chemopreventive target for benzo[*a*]pyrene-initiated human esophageal cancer. *Cancer Lett.* 2007; 246(1–2):109–114. [PubMed: 16530937]
135. Burczynski ME, Penning TM. Genotoxic polycyclic aromatic hydrocarbon *ortho*-quinones generated by aldo-keto reductases induce CYP1A1 via nuclear translocation of the aryl hydrocarbon receptor. *Cancer Res.* 2000; 60(4):908–915. [PubMed: 10706104]
136. Ciolino HP, Yeh GC. Inhibition of aryl hydrocarbon-induced cytochrome P-450 1A1 enzyme activity and CYP1A1 expression by resveratrol. *Mol. Pharmacol.* 1999; 56(4):760–767. [PubMed: 10496959]
137. Chun YJ, Kim MY, Guengerich FP. Resveratrol is a selective human cytochrome P450 1A1 inhibitor. *Biochem. Biophys. Res. Commun.* 1999; 262(1):20–24. [PubMed: 10448061]
138. Chang TK, Chen J, Lee WB. Differential Inhibition and Inactivation of human CYP1 enzymes by *trans*-resveratrol: Evidence for mechanism-based inactivation of CYP1A2. *J. Pharmacol. Exp. Ther.* 2001; 299(3):874–882. [PubMed: 11714871]
139. Piver B, Berthou F, Dreano Y, Lucas D. Abstracts from the 8th European ISSX Meeting, Dijon, France, April 27– May 1, 2003. Comparison of inhibitory potencies of resveratrol and *epsylon*-viniferin on human cytochrome P450 enzymes. *Drug Metab Rev.* 2003; 35(Suppl. 1):115.
140. Piver B, Berthou F, Dreano Y, Lucas D. Differential inhibition of human cytochrome P450 enzymes by *epsilon*-viniferin.; the dimer of resveratrol: comparison with resveratrol and polyphenols from alcoholized beverages. *Life Sci.* 2003; 73(9):1199–1213. [PubMed: 12818727]
141. Casper RF, Quesne M, Rogers IM, Shirota T, Jolivet A, Milgrom E, Savouret JF. Resveratrol has antagonist activity on the aryl hydrocarbon receptor: implications for prevention of dioxin toxicity. *Mol. Pharmacol.* 1999; 56(4):784–790. [PubMed: 10496962]
142. Baker JR, Satarug S, Reilly PE, Edwards RJ, Ariyoshi N, Kamataki T, Moore MR, Williams DJ. Relationships between non-occupational cadmium exposure and expression of nine cytochrome P450 forms in human liver and kidney cortex samples. *Biochem. Pharmacol.* 2001; 62(6):713–721. [PubMed: 11551516]
143. Baker JR, Satarug S, Edwards RJ, Moore MR, Williams DJ, Reilly PE. Potential for early involvement of CYP isoforms in aspects of human cadmium toxicity. *Toxicol. Lett.* 2003; 137(1–2):85–93. [PubMed: 12505434]
144. Wei C, Caccavale RJ, Weyand EH, Chen S, Iba MM. Induction of CYP1A1 and CYP1A2 expressions by prototypic and atypical inducers in the human lung. *Cancer Lett.* 2002; 178(1): 25–36. [PubMed: 11849738]
145. Wen X, Walle UK, Walle T. 5,7-Dimethoxyflavone downregulates CYP1A1 expression and benzo[*a*]pyrene-induced DNA binding in Hep G2 cells. *Carcinogenesis*. 2005; 26(4):803–809. [PubMed: 15661813]
146. Port JL, Yamaguchi K, Du B, De Lorenzo M, Chang M, Heerdt PM, Kopelovich L, Marcus CB, Altorki NK, Subbaramaiah K, Dannenberg AJ. Tobacco smoke induces CYP1B1 in the aerodigestive tract. *Carcinogenesis*. 2004; 25(11):2275–2281. [PubMed: 15297370]
147. Walle T, Walle UK. Novel methoxylated flavone inhibitors of cytochrome P450 1B1 in SCC-9 human oral cancer cells. *J. Pharm. Pharmacol.* 2007; 59(6):857–862. [PubMed: 17637178]
148. Courter LA, Pereira C, Baird WM. Diesel exhaust influences carcinogenic PAH-induced genotoxicity and gene expression in human breast epithelial cells in culture. *Mutat. Res.* 2007; 625(1–2):72–82. [PubMed: 17612574]

149. Kisselev P, Schwarz D, Platt KL, Schunck WH, Roots I. Epoxidation of benzo[*a*]pyrene-7,8-dihydrodiol by human CYP1A1 in reconstituted membranes. *Eur. J. Biochem.* 2002; 269(7): 1799–1805. [PubMed: 11952781]
150. Lamb DC, Kelly DE, Baldwin BC, Kelly SL. Differential inhibition of human CYP3A4 and *Candida albicans* CYP51 with azole antifungal agents. *Chem.-Biol. Interact.* 2000; 125(3):165–175. [PubMed: 10731517]
151. Mammen JS, Pittman GS, Li Y, Abou-Zahr F, Bejjani BA, Bell DA, Strickland PT, Sutter TR. Single amino acid mutations, but not common polymorphisms, decrease the activity of CYP1B1 against (–)benzo[*a*]pyrene-7*R-trans*-7,8-dihydrodiol. *Carcinogenesis.* 2003; 24(7):1247–1255. [PubMed: 12807732]
152. Schwarz D, Kisselev P, Roots I. CYP1A1 genotype-selective inhibition of benzo[*a*]pyrene activation by quercetin. *Eur. J. Cancer.* 2005; 41(1):151–158. [PubMed: 15618000]
153. Li DN, Seide IA, Pritchard MP, Wolf CR, Friedberg T. Polymorphisms in P450 CYP1B1 affect the conversion of estradiol to the potentially carcinogenic metabolite 4-hydroxyestradiol. *Pharmacogenetics.* 2000; 10(4):343–353. [PubMed: 10862525]

<u>Ractions:</u>	<u>Enzymes*:</u>
C ^{7,8} -epoxide formation 1	P450 1A1 , 1A2, 1B1 , 2B6, 2C19, 2E1, 3A4
Hydrolysis of epoxide 2	Epoxide hydrolase X1(EPHX1)
C ^{9,10} -epoxidation of C ^{7,8} -dihydrodiol 3	P450 1A1 , 1A2, 1B1 , 2B6, 2C9, 2C19, 3A4 , 2S1 Peroxidase (PHS, 15-lipoxygenase)

Oxidation of C ^{7,8} -dihydrodiol to C ^{7,8} -dione 4	AKR 1A1 , 1B1, 1B10, 1C1-1C4
C ^{3,7,or 9} -hydroxylations 5	P450 1A1 , 1B1, 2B6, 2C8, 2C9 , 2C18, 2C19 , 2E1, 3A4
Glucuronidation of hydroxylated metabolites C ⁵ -OH, C ⁷ -OH . C ⁹ -OH . C ¹² -OH, B[a]P- <i>trans</i> -7,8-dihydrodiol, B[a]P-3,6,-quinol 6	UGT1A1, 1A6, 1A7, 1A9, 1A10, 2A1, 2A2, 2A7,
O-sulfate conjugates formation of hydroxylated metabolites: 7 C ⁷ -OH, C ⁹ -OH, C ⁷ ,C ⁸ -catechol (7-O-sulfate formation)	SULT 1A1 , 1A3, 1E1

*Bold font in the table designates major enzyme(s) catalyzing the reaction(s).

Figure 1.
Biotransformation and Toxicity of Benzo[*a*]pyrene by P450 enzymes.

FREE! Human P450 Metabolism Database

Start at www.gentest.com

Click on **Human P450 Metabolism Database** to find a free, web-searchable database that contains a collection of information on human cytochrome P450 metabolism. Data collected from hundreds of references summarize many human cytochrome P450 reactions and interactions.

Good Reasons to Use This Database!

- 1 The main page introduces you...** to the database which was created (and continues to be updated) by Professor Slobodan Rendic of the University of Zagreb. Completion of a simple registration form allows free instant entry into the database.
- 2 Search through hundreds...** of references that summarize many human cytochrome P450 reactions and interactions. Information about human PGP (MDR1) is also included. The information is organized by enzyme, therapeutic area, chemical substance, reaction, and type (substrate, inhibitor, activator, or inducer).
- 3 Get a detailed view of the data...** in easy to read tables. Complete reference citation information is included for every data entry.
- 4 A detailed User's Guide helps you...** quickly learn to utilize the search and display features of the database to find the information you need.

Figure 2.

Free Web-searchable P450 metabolism database sponsored by Gentest, USA, 1998–2003.

Table 1

Cytochrome P450 Enzymes* - Examples of Inducers, Substrates and Reactions as Published in 1989–1990.*

P450 family	Subfamily	Enzyme	Inducing agents	Substrate (examples)	Reference
1	A	P-450 IA1 (human and rodent enzyme)	PAHs (benzo[<i>a</i>]pyrene, benz[<i>a</i>]anthracene), isosafrole, dioxins, 3-methylcholanthrene	Benzo(<i>a</i>)pyrene, cyclic amines, 7-ethoxyresorufin O-deethylation,	[2,3,4]
		P-450 IA2 (human and rodent enzyme)		PhIP N-hydroxylation and 4'-hydroxylation,	
				PCBs, azobenzene, aryl- and heterocyclic amines activation	
2	A	P-450 IIA1 (rodent enzyme)	phenobarbital	steroid hydroxylations,	[5]
		P-450 IIA2 (rodent enzyme)		tobacco-related nitrosamines	
B		P-450 IIB1 (rodent enzyme)	phenobarbital	testosterone to yield the 16 α -hydroxy, 16 β -hydroxy, and 17-keto metabolites,	[6]
		P-450 IIB2 (rodent enzyme)		cyclophosphamide,	
C		P-450 IIC11 (rodent enzyme)	phenobarbital	androstenedione 16 α -hydroxylase, benzo[<i>a</i>]pyrene - 9,10-dihydrodiol and -7,8-dihydrodiol formation	[7,8]
		P-450 IID1 (rodent enzyme)		(+)-bufuralol 1'-hydroxylation,	
				debrisoquine 4-hydroxylation	
D		P-450 IID6 (human enzyme)		(+)-bufuralol 1'-hydroxylation,	[9,10]
				debrisoquine 4-hydroxylation and hydroxylation of 20 different drugs (basic amines)	
				ethanol, halothane,	
E		P-450 IIE1 (human and rodent enzyme)	ethanol, acetone, isoniazid, pyridine	chlorzoxazone, benzene, aniline,	[11]
				paracetamol, shortchain nitrosamines activation,	
				N-nitrosodimethylamine (NDMA) demethylation,	
F		P-450 IIF1 (human enzyme)	ethanol, acetone, isoniazid, pyridine	N-nitrosomethylbenzylamine, p-nitrophenol, phenol	[12]
F		P-450 IIF1 (human enzyme)	ethanol, acetone, isoniazid, pyridine	7-ethoxycoumarin dealkylation, 3-methylindole activation,	[13,14]

P450 family	Subfamily	Enzyme	Inducing agents	Substrate (examples)	Reference
3	A	P-450 IIIA1	16 α -carbonitrile	4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) activation	[15,16]
		P-450 IIIA2	(PCN), clotrimazole, cyclosporine, troleandomycin	macrolide antibiotics,	
		P-450 IIIA3 (human enzyme)		testosterone hydroxylations,	
		P-450 IIIA4 (human enzyme)	nifedipine, rifampicin, barbiturates, steroids	tianeptine activation	
				nifedipine (1,4-) oxidation,	
				macrolide antibiotics (erythromycin and troleandomycin) N-demethylation,	
				testosterone, cortisol, progesterone, and androstenedione	
				6 β -hydroxylation,	
				17 β -estradiol and 17 α -	
				ethynylestradiol C2-hydroxylation,	
4	A			quinidine N-oxygenation and 3-hydroxylation,	[3,17, 18 ^{**} , 19]
				dehydroepiandrosterone 3-sulfate	
				16 α -hydroxylation,	
				(<i>R</i>)-warfarin 10-hydroxylation,	
				aflatoxins B1 and G1 activation,	
				PAH-diol activations	
				sterigmatocystin activation,	
				6-aminochrysene activation,	
				tris-(2,3-dibromopropyl)phosphate activation	
5	A	P-450 IVA1 (rodent enzyme)	clofibrate	fatty acids ω - and (ω -1)-hydroxylation	[20,21]
		P-450 IVA1		prostaglandins E1 and F2 α , ω -hydroxylation	
		3 (rodent enzyme)			
5	A	P-450 V	phorbol esters	Prostaglandin H2	[22]

* Enzyme nomenclature is as reported and/or as recommended [1]

** Reference 12 in text.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Table 2

Examples of Interactions of Benzo[a]pyrene (B[a]P) with Human Cytochrome P450 (P450, CYP) Enzymes as Substrate, Inhibitor and/or Inducer. (Data Collected up to 2008).

Enzyme	Chemical	Reaction	Type	Remarks	References
1A1	B[a]P	9,10-Dihydrodiol formation	Substrate	Low activity	[23,24]
1A1	B[a]P	4,5-Dihydrodiol formation	Substrate		[23,24]
1A1	B[a]P	1,6-Dione (quinone) formation	Substrate	Low activity	[23,24,25]
1A1	B[a]P	3,6-Dione (quinone) formation	Substrate	Low activity	[23,24]
1A1	B[a]P	6,12-Dione (quinone) formation	Substrate	Low activity	[23]
1A1	B[a]P	Oxidation	Substrate	Low activity, medium activity, or high activity, high efficiency, metabolic activation, toxicologically relevant induction by TCDD, potent metabolic activation at low conc.	[26,27,28,28,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47,48,49,50]
1A1	B[a]P	7,8-Dihydroxy-7,8-dihydro- (7,8-dihydrodiol) formation	Substrate	Low activity	[23,24,25,33,34,43,44,45,51]
1A1	B[a]P	Hydroxylation, 3-(low K_m , or medium K_m , medium activity, or high activity), 9-, 10-, 1-	Substrate		[23,24,25,33,34,52,53,54,55,56,57,58,560,61,62,63,64]
1A1	B[a]P	<i>trans</i> -7,8-Dihydroxy-7,8-dihydro-(7,8-dihydrodiol) formation	Substrate	Very low activity	[25]
1A1	B[a]P	<i>trans</i> -7,8-Dihydroxy-9,10-epoxy-7,8,9,10-tetrahydro-formation	Substrate	Metabolic activation, major enzyme in RL95-2 uterine endometrial cells	[49]
1A1	<i>trans</i> -(+)-B[a]P-7,8-dihydrodiol	<i>cis</i> -(<i>syn</i>)-7,8-Dihydroxy-9,10-epoxy-7,8,9,10-tetrahydro-, (<i>cis</i> -Diolepoxide, DE1), formation	Substrate		[149]
1A1	<i>trans</i> -(+)-B[a]P-7,8-dihydrodiol	<i>trans</i> -(<i>anti</i>)-7,8-Dihydroxy-9,10-epoxy-7,8,9,10-tetrahydro-, (<i>trans</i> -Diolepoxide, DE2), formation	Substrate		[149]
1A1	<i>trans</i> -(-)-B[a]P-7,8-dihydrodiol	<i>cis</i> -(<i>syn</i>)-7,8-Dihydroxy-9,10-epoxy-7,8,9,10-tetrahydro-, (<i>cis</i> -Diolepoxide, DE1), formation	Substrate		[149]
1A1	<i>trans</i> -(-)-B[a]P-7,8-dihydrodiol	<i>trans</i> -(<i>anti</i>)-7,8-Dihydroxy-9,10-epoxy-7,8,9,10-tetrahydro-, (<i>trans</i> -Diolepoxide, DE2), formation	Substrate		[149]
1A1, GSTP1	B[a]P	Oxidation and GSH-conjugation	Substrate	Decreased mutagenicity in coexpressed V79MZ cells	[48]
1A1.1	B[a]P	<i>trans</i> -7,8-Dihydroxy-7,8-dihydro- (7,8-dihydrodiol) formation	Substrate		[23,24,33,34,43,44,45,51]
1A1.1	B[a]P	1,6-Dione (quinone) formation	Substrate		[23,24,33,34,43,44,45,51]
1A1.1	B[a]P	3-, 9-, 7,8-, 9,10- Hydroxylation and 4,5-diol formation, 1,6-, 3,6- and 6,12-dione formation	Substrate		[54,55,56,57]
1A1.1	B[a]P	7,8- and 9,10-Dihydrodiol formation	Substrate		[65,66,67,68,69,70,71,72,73,74]
1A1.1	B[a]P	Hydroxylation, C3-	Substrate	Low K_m , high activity	[75]
1A1.1	<i>trans</i> -(-)-B[a]P-7,8-dihydrodiol	<i>trans</i> -(<i>anti</i>)-7,8-Dihydroxy-9,10-epoxy-7,8,9,10-tetrahydro-, (<i>trans</i> -Diolepoxide, DE2), formation	Substrate		[152]
1A1.2	B[a]P	9,10-Dihydrodiol formation	Substrate	Low activity	[23,24,33,34,43,44,45,51]

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Enzyme	Chemical	Reaction	Type	Remarks	References
1A1.2	B[a]P	3,6-Dione (quinone) formation	Substrate		[23,24,33,34,43,51]
1A1.2	B[a]P	3-, 9-, 7,8-, 9,10- Hydroxylation and 4,5-diol formation. 1,6-, 3,6- and 6,12-dione formation	Substrate		[54,55,56,57]
1A1.2	B[a]P	7,8- and 9,10-Dihydrodiol formation	Substrate		[65,66,67,68,69,70,71]
1A1.2	B[a]P	Hydroxylation, C3-	Substrate	Low K_m , high activity	[75]
1A1.2	<i>trans</i> -(−)-B[a]P-7,8-dihydrodiol	<i>trans</i> -(<i>anti</i>)-7,8-Dihydroxy-9,10-epoxy-7,8,9,10-tetrahydro-, (<i>trans</i> -Diolepoxide, DE2), formation	Substrate		[152]
1A1.4	B[a]P	4,5-Dihydrodiol formation	Substrate		[23,24,33,34,43,44,45,51]
1A1.4	B[a]P	6,12-Dione (quinone) formation	Substrate		[23,24,33,34,43,44,45,51]
1A1.4	B[a]P	3-, 9-, 7,8-, 9,10- Hydroxylation and 4,5-diol formation. 1,6-, 3,6- and 6,12-dione formation	Substrate		[54,55,56,57]
1A1.4	<i>trans</i> -(−)-B[a]P-7,8-dihydrodiol	<i>trans</i> -(<i>anti</i>)-7,8-Dihydroxy-9,10-epoxy-7,8,9,10-tetrahydro-, (<i>trans</i> -Diolepoxide, DE2), formation	Substrate		[152]
1A2	B[a]P	Oxidation	Substrate	Metabolic activation at low concentration, induced by TCDD, relevant for both metabolic activation and deactivation	[26,27,28,28,30,31,32,46]
1A2	B[a]P	3-, 9-, 7-Hydroxylation and 7,8-, 9,10-, 4,5-dihydrodiol formation	Substrate	Low activity	[23,24,25,52,53,54,55,56,57]
1A2	B[a]P	9,10-Dihydrodiol formation	Substrate	Very low activity	[25]
1A2	B[a]P	1,6-Dione (quinone) formation	Substrate	Low activity	[25]
1A2	B[a]P	3,6-Dione (quinone) formation	Substrate	Low activity	[25]
1A2	B[a]P	6,12-Dione (quinone) formation	Substrate	Low activity	[25]
1B1	B[a]P	<i>trans</i> -7,8-Dihydroxy-7,8-dihydro-(7,8-dihydrodiol) formation	Substrate	Low activity, medium activity, or high activity, major enzyme	[25,26,27,28,28,30,31,32,33,33,34,43,44,45]
1B1	B[a]P	Hydroxylation, C3-	Substrate		[33,34]
1B1	B[a]P	<i>trans</i> -7,8-Dihydroxy-9,10-epoxide formation	Substrate	Medium K_m , high activity, high efficiency, metabolic activation	[25,26,27,28,28,30,31,32,35,36,37,38,39,40,41,42,82]
1B1	B[a]P	9,10-Dihydrodiol formation	Substrate	Low activity	[25]
1B1	B[a]P	1,6-Dione (quinone) formation	Substrate	Low activity	[25]
1B1	B[a]P	3,6-Dione (quinone) formation	Substrate	Low activity	[25]
1B1	B[a]P	Hydroxylation 3-, 9-, 7-	Substrate		[25]
1B1	B[a]P	Oxidation	Substrate	Weak metabolic activation	[49,83]
1B1	<i>trans</i> -(−)-B[a]P-7,8-diol	<i>trans</i> -(<i>anti</i>)-7,8-Dihydroxy-9,10-epoxy-7,8,9,10-tetrahydro- form. (<i>trans</i> -Diolepoxide form.) and tetrol (RTTC) form.	Substrate		[81,151]
1B1	<i>trans</i> -(−)-B[a]P-7,8-diol	Tetrol formation	Substrate		[153]
1B1.1	B[a]P	<i>trans</i> -7,8-Dihydroxy-7,8-dihydro-(7,8-dihydrodiol) formation	Substrate	Medium K_m , medium activity	[84]

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Enzyme	Chemical	Reaction	Type	Remarks	References
1B1.1	B[a]P	Hydroxylation, C3-	Substrate		[84]
1B1.1	B[a]P	4,5-Dihydrodiol formation	Substrate		[84]
1B1.1	B[a]P	Oxidation	Substrate	Metabolic activation	[26,27,28,30,31,32]
1B1.1	trans-($\rightarrow$)-B[a]P-7,8-diol	Tetrol formation	Substrate		[153]
1B1 432L,453S	trans-($\rightarrow$)-B[a]P-7,8-diol	Tetrol formation	Substrate		[153]
1B1.2	B[a]P	trans-7,8-Dihydroxy-7,8-dihydro-(7,8-dihydrodiol) formation	Substrate	Medium K_m , low activity	[84]
1B1.2	B[a]P	Oxidation	Substrate	Metabolic activation	[26,27,28,28,30,31,32]
1B1.3	B[a]P	trans-7,8-Dihydroxy-7,8-dihydro-(7,8-dihydrodiol) formation	Substrate	Medium K_m , medium activity	[84]
1B1.3	trans-($\rightarrow$)-B[a]P-7,8-diol	Tetrol formation	Substrate		[153]
1B1.3	B[a]P	Oxidation (activation)	Substrate	Metabolic activation	[26,27,28,28,30,31,32]
1B1.4	B[a]P	trans-7,8-Dihydroxy-7,8-dihydro- (7,8-dihydrodiol) formation	Substrate	Medium K_m , low activity	[84]
1B1.6	B[a]P	trans-7,8-Dihydroxy-7,8-dihydro- (7,8-dihydrodiol) formation	Substrate	Medium K_m , medium activity	[84]
1B1.6	B[a]P	Oxidation	Substrate	Metabolic activation	[26,27,28,28,30,31,32]
1B1.7	B[a]P	trans-7,8-Dihydroxy-7,8-dihydro- (7,8-dihydrodiol) formation	Substrate	Medium K_m , low activity	[84]
2B6	B[a]P	Hydroxylation, C7- and 7,8-diol formation	Substrate		[54,55,56,57]
2C18	B[a]P	3-Hydroxylation and dihydrodiols formation	Substrate	Low activity	[52,53,54,55,56,57]
2C19	B[a]P	3- and 9- Hydroxylation and 7,8-, 9,10-, 4,5- dihydrodiols formation (major enzyme)	Substrate	Low activity	[52,53,54,55,56,57]
2C19	B[a]P	Oxidation	Substrate	Weak metabolic activation	[46]
2C8	B[a]P	3- and 9- Hydroxylation and 7,8-, 9,10-, 4,5- dihydrodiol formation	Substrate		[52,53,54,55,56,57]
2C9	B[a]P	Oxidation	Substrate	Weak metabolic activation	[46,85,86]
2C9	B[a]P	3- Hydroxylation (major enzyme), 9-, 7- hydroxylation and 7,8-dihydrodiol formation (major enzyme), 9,10-, 4,5 – dihydrodiol formation	Substrate		[52,53,54,55,56,57]
2D6	B[a]P	Oxidation	Substrate	Weak metabolic activation	[553]
2E1	B[a]P	Oxidation	Substrate	Metabolic activation	[33,34,35,36,37,38,39,40,41,42]
2E1	B[a]P	3-, 9- Hydroxylation and 7,8-, 9,10-, 4,5-dihydrodiol formation	Substrate	Low activity	[52,53,54,55,56,57]
3A4	B[a]P	3- Hydroxylation (major enzyme), 9- hydroxylation and 7,8-, 9,10-, 4,5- dihydrodiol formation	Substrate	Low activity	[17,33,34,52,53,54,55,56,57,76,77,78,79,80,150]
3A4	B[a]P	Oxidation	Substrate	Metabolic activation	[46,86]
19 (Aromatase)	B[a]P		Inhibitor		[87,88]
1A1	B[a]P		Inhibitor	Potent inhibitor, direct competitive inhibitor	[89,90,91]
1A1	B[a]P C3-hydroxy		Inhibitor	Potent inhibitor	[89]

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Enzyme	Chemical	Reaction	Type	Remarks	References
1A1	B[a]P C9-hydroxy		Inhibitor	Potent inhibitor	[89]
1A2	B[a]P C3-hydroxy		Inhibitor	Potent inhibitor	[89]
1A2	B[a]P C9-hydroxy		Inhibitor	Potent inhibitor	[89]
1A2	B[a]P		Inhibitor	Potent mechanism-based inhibitor	[89,91]
1B1	B[a]P		Inhibitor	Potent inhibitor, direct competitive inhibitor	[89,90,91]
1B1	B[a]P C3-hydroxy		Inhibitor	Potent inhibitor	[89]
1B1	B[a]P C9-hydroxy		Inhibitor	Potent inhibitor	[89]
3A4	B[a]P		Inhibitor	Medium inhibitor, IC ₅₀ >10 μM	[92]
19A1 (Aromatase)	B[a]P		Inducer	Weak inducer	[93]
1A	B[a]P		Inducer	Potent inducer, inducer of activity	[94,95]
1A1	B[a]P		Inducer	AhR agonist, potent inducer, inducer of mRNA expression, inducer of protein level, inducer of activity in BEAS-2B, oral SCC-9, HEP G2 cells, and RL95-2 c cells, autoinduction, weak inducer of mRNA expression in HET-1A cells	[49,62,90,96,98,99,100,101,102,103,104,105,106,107,108,109,110,111,112,113,114,115,116,117,118,119,120,121,122,125,126,127,128,129,130,131,132,133,134,135]
1A1	B[a]P 3,6-quinone, 3,6-BPQ		Inducer	Inducer of mRNA expression in HepG2 cells	[97,135]
1A1	B[a]P 7,8-quinone, 7,8-BPQ		Inducer	Potent inducer of mRNA expression in HepG2 cells	[135]
1A1	B[a]P 1,6-quinone, 1,6-BPQ		Inducer	Inducer of mRNA expression in HepG2 cells	[135]
1A1	B[a]P 6,12-quinone, 6,12-BPQ		Inducer	Inducer of mRNA expression in HepG2 cells	[135]
1A2	B[a]P		Inducer	Lower toxicological potential	[96,98,99,104,105,106,113,123,124,136,137,138,139,140,141,142,143,144,145]
1B1	Benzo[a]pyrene, B[a]P		Inducer	AhR agonist, inducer of mRNA expression in BEAS-2B cells, inducer of mRNA expression in HET-1A cells and oral SCC-9 cells, inducer of protein expression in HET-1A cells, oral SCC-9, RL95-2 cells and lung epithelial cells, high toxicological potential, no inducer in Hep G2 cells, no inducer of activity in and RL95-2 c cells	[49,62,64,90,96,113,115,116,117,118,119,120,122,125,126,127,129,131,132,133,134,146,147,148]
1B1	Benzo[a]pyrene 3,6-quinone, 3,6-BPQ		Inducer	Inducer of mRNA expression in HepG2 cells	[97]
1B1	Benzo[a]pyrene 1,6-quinone, 1,6-BPQ		Inducer	Inducer of mRNA expression in HepG2 cells	[97]
4F3B	Benzo[a]pyrene 3,6-quinone, 3,6-BPQ		Inducer	Inducer of mRNA expression in HepG2 cells	[97]

Table 3

Examples of Kinetic Data on Interactions of Benzo[a]pyrene (B[a]P) with Human Cytochrome P450 (P450, CYP) Enzymes as Substrate, Including Metabolic Activation Without and in the Presence of Inhibitors. (Data Collected up to 2008).

Enzyme	Model used	Substrate	Reaction	Inhibitor /Ligand	K_m (μ M); (S_{50} (μ M))	V_{max} k_{cat} (nmol/min/nmol of CYP; l/min, or as specified)	Enzyme efficiency V_{max}/K_m (ml/min/nmol P450, or as specified)	K_i (K_I); (μ M, or as specified)	IC_{50} (μ M, or as specified)	Reference
CYP1A1	<i>Escherichia coli</i> expressing human CYP, membranes	B[a]P	<i>trans</i> -7,8-Dihydroxy-7,8-dihydro- d) formation (metabolic activation)			293±43 <i>umu</i> gene expression units/min/nmol				[51]
CYP1A1	<i>E. coli</i> expressing human CYP, membranes, +epoxide hydrolase	B[a]P	<i>trans</i> -7,8-Dihydroxy-7,8-dihydro- (7,8-dihydrodiol) formation			0.27±0.05				[51]
CYP1A2	<i>E. coli</i> expressing human CYP, membranes, +epoxide hydrolase	B[a]P	<i>trans</i> -7,8-Dihydroxy-7,8-dihydro- (7,8-dihydrodiol) formation			0.02±0.01				[51]
CYP1B1	<i>E. coli</i> expressing human CYP, membranes	B[a]P	<i>trans</i> -7,8-Dihydroxy-7,8-dihydro- (7,8-dihydrodiol) formation (metabolic activation)			410±46 <i>umu</i> gene expression units/min/nmol				[51]
CYP1B1	<i>E. coli</i> expressing human CYP, membranes, +epoxide hydrolase	B[a]P	<i>trans</i> -7,8-Dihydroxy-7,8-dihydro- (7,8-dihydrodiol) formation			2.69±0.22				[51]
CYP1A1	<i>E. coli</i> expressing human CYP, purified	B[a]P	1,6-Dione (quinone) formation			1.41				[24]
CYP1A1	<i>E. coli</i> expressing human CYP, purified	B[a]P	3,6-Dione (quinone) formation			0.75				[24]
CYP1A1	<i>E. coli</i> expressing human CYP, purified	B[a]P	4,5-Dihydrodiol formation			0.5				[24]
CYP1A1	<i>E. coli</i> expressing human CYP, purified	B[a]P	7,8-Dihydrodiol formation			1.9				[24]
CYP1A1	<i>E. coli</i> expressing human CYP, purified	B[a]P	9,10-Dihydrodiol formation			2.45				[24]
CYP1A1	<i>E. coli</i> expressing human CYP, purified	B[a]P	C3-Hydroxylation,		15	2.5				[24]
CYP1A1	<i>E. coli</i> expressing human CYP, purified	B[a]P	C3-Hydroxylation,			1.77				[24]
CYP1A1	<i>E. coli</i> expressing human CYP, purified	B[a]P	C9-Hydroxylation,			0.77				[24]
CYP1A2	<i>E. coli</i> expressing human CYP, purified	B[a]P	4,5-Dihydrodiol formation			0.05				[24]
CYP1A2	<i>E. coli</i> expressing human CYP, purified	B[a]P	7,8-Dihydrodiol formation			0.08				[24]
CYP1A2	<i>E. coli</i> expressing human CYP, purified	B[a]P	9,10-Dihydrodiol formation			0.05				[24]
CYP1A1	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes, +NADPH-P450 reductase,	<i>trans</i> -($\pm$)-B[a]P-7,8-dihydrodiol	<i>trans</i> -(<i>anti</i>)-7,8-Dihydroxy-9,10-epoxy-7,8,9,10-tetrahydro-formation (trans-diol epoxide or DE2 formation)		1.2±0.2	2.5±0.1				[149]

Enzyme	Model used	Substrate	Reaction	Inhibitor/Ligand	K_m (μ M); (S_{50} (μ M))	V_{max} (nmol/min/nmol of CYP; l/min, or as specified)	Enzyme efficiency (V_{max}/K_m (ml/min/nmol P450, or as specified)	K_i (μ M); or as specified)	IC_{50} (μ M, or as specified)	Reference
CYP1A1	purified, reconstituted into Ole2PtdCho (phospholipid vesicle membranes) Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes, +NADPH-P450 reductase, purified, reconstituted into Ole2PtdCho/PtdSer (2:1) phospholipid vesicle membranes	<i>trans</i> -(−)-B[a]P-7,8-dihydrodiol	<i>trans</i> -(<i>anti</i>)-7,8-Dihydroxy-9,10-epoxy-7,8,9,10-tetrahydro-formation (trans-diol epoxide or DE2 formation)		25.1±7.2	32.7±6.3				[149]
CYP1A1	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes, +NADPH-P450 reductase, purified, reconstituted, Ole2PtdCho/PtdIns (2:1) phospholipid vesicle membranes	<i>trans</i> -(−)-B[a]P-7,8-dihydrodiol	<i>trans</i> -(<i>anti</i>)-7,8-Dihydroxy-9,10-epoxy-7,8,9,10-tetrahydro-formation (trans-diol epoxide or DE2 formation)		6.7±1.4	18.0±1.6				[149]
CYP1A1	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes, +NADPH-P450 reductase, purified, reconstituted, PtdCho/PtdEtn/PA (2:1:0.06) phospholipid vesicle membranes	<i>trans</i> -(−)-B[a]P-7,8-dihydrodiol	<i>trans</i> -(<i>anti</i>)-7,8-Dihydroxy-9,10-epoxy-7,8,9,10-tetrahydro-formation (trans-diol epoxide or DE2 formation)		4.9±1.3	7.3±0.7				[149]
CYP1A1	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes, +NADPH-P450 reductase, purified, reconstituted into Ole2PtdCho/Ole2PtdEtn (2:1) phospholipid vesicle membranes	<i>trans</i> -(−)-B[a]P-7,8-dihydrodiol	<i>trans</i> -(<i>anti</i>)-7,8-Dihydroxy-9,10-epoxy-7,8,9,10-tetrahydro-formation (trans-diol epoxide or DE2 formation)		9.7±2.2	19.9±2.2				[149]
CYP1A1	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes, +NADPH-P450 reductase, purified, reconstituted into Ole2PtdCho/Ela2PtdEtn (2:1) phospholipid vesicle membranes	<i>trans</i> -(−)-B[a]P-7,8-dihydrodiol	<i>trans</i> -(<i>anti</i>)-7,8-Dihydroxy-9,10-epoxy-7,8,9,10-tetrahydro-formation (trans-Diol epoxide or DE2 formation)		1.6±0.1	3.7±0.1				[149]
CYP1A1	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes, +NADPH-P450 reductase, purified, reconstituted into Ole2PtdCho phospholipid vesicle membranes	<i>trans</i> -(−)-B[a]P-7,8-dihydrodiol	<i>cis</i> -(<i>syn</i>)-7,8-Dihydroxy-9,10-epoxy-7,8,9,10-tetrahydro-formation (<i>cis</i> -Diol epoxide, or DE1 formation)		1.2±0.3	0.6±0.1				[149]
CYP1A1	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes, +NADPH-P450 reductase, purified, reconstituted into Ole2PtdCho/PtdSer (2:1) phospholipid vesicle membranes	<i>trans</i> -(−)-B[a]P-7,8-diol	<i>cis</i> -(<i>syn</i>)-7,8-Dihydroxy-9,10-epoxy-7,8,9,10-tetrahydro-formation (<i>cis</i> -diol epoxide, or DE1 formation)		17.3±4.2	3.2±0.4				[149]
CYP1A1	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes, +NADPH-P450 reductase, purified, reconstituted into Ole2PtdCho/PtdIns (2:1) phospholipid vesicle membranes	<i>trans</i> -(−)-B[a]P-7,8-diol	<i>cis</i> -(<i>syn</i>)-7,8-Dihydroxy-9,10-epoxy-7,8,9,10-tetrahydro-formation (<i>cis</i> -diol epoxide, or DE1 formation)		6.4±1.5	2.3±0.3				[149]
CYP1A1	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes, +NADPH-P450 reductase,	<i>trans</i> -(−)-B[a]P-7,8-dihydrodiol	<i>cis</i> -(<i>syn</i>)-7,8-Dihydroxy-9,10-epoxy-7,8,9,10-tetrahydro-formation (<i>cis</i> -Diol epoxide, or DE1 form)		6.0±2.1	0.8±0.1				[149]

Enzyme	Model used	Substrate	Reaction	Inhibitor/Ligand	K_m (μM); (S_{50} (μM))	V_{max} ($\text{nmol/min/nmol of CYP; l/min, or as specified}$)	Enzyme efficiency (K_m/V_{max} ($\text{ml/nmol P450, or as specified}$))	K_i (μM); (K_I (μM); or as specified)	IC_{50} (μM , or as specified)	Reference
CYP1A1	purified, reconstituted into PtdCho/PtdEtn/PA (2:1:0.06) phospholipid vesicle membranes Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes, +NADPH-P450 reductase, purified, reconstituted into Ole2PtdCho/Ole2PtdEtn (2:1) phospholipid vesicle membranes	<i>trans</i> (-)-B[a]P-7,8-dihydrodiol	<i>cis</i> -(<i>syn</i>)-7,8-Dihydroxy-9,10-epoxy-7,8,9,10-tetrahydro-formation (<i>cis</i> -diol epoxide, or DE1 formation)		7.5±1.6	3.2±0.3				[149]
CYP1A1	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes, +NADPH-P450 reductase, purified, reconstituted into Ole2PtdCho/Ela2PtdEtn (2:1)	<i>trans</i> (-)-B[a]P-7,8-dihydrodiol	<i>cis</i> -(<i>syn</i>)-7,8-Dihydroxy-9,10-epoxy-7,8,9,10-tetrahydro-formation (<i>cis</i> -diol epoxide, or DE1 formation)		2.7±0.3	0.8±0.1				[149]
CYP1A1	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes, +NADPH-P450 reductase, purified, reconstituted into Ole2PtdCho phospholipid vesicle membranes	<i>trans</i> (+)-B[a]P-7,8-dihydrodiol	<i>trans</i> -(<i>anti</i>)-7,8-Dihydroxy-9,10-epoxy-7,8,9,10-tetrahydro-formation (<i>trans</i> -diol epoxide or DE2 formation)		11.4±3.7	0.5±0.1				[149]
CYP1A1	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes, +NADPH-P450 reductase, purified, reconstituted into Ole2PtdCho/PtdSer (2:1) phospholipid vesicle membranes	<i>trans</i> (+)-B[a]P-7,8-dihydrodiol	<i>trans</i> -(<i>anti</i>)-7,8-Dihydroxy-9,10-epoxy-7,8,9,10-tetrahydro-formation (<i>trans</i> -diol epoxide or DE2 formation)		14.3±3.2	0.9±0.12				[149]
CYP1A1	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes, +NADPH-P450 reductase, purified, reconstituted into Ole2PtdCho/PtdIns (2:1) phospholipid vesicle membranes	<i>trans</i> (+)-B[a]P-7,8-dihydrodiol	<i>trans</i> -(<i>anti</i>)-7,8-Dihydroxy-9,10-epoxy-7,8,9,10-tetrahydro-formation (<i>trans</i> -diol epoxide or DE2 formation)		5.7±0.9	0.7±0.04				[149]
CYP1A1	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes, +NADPH-P450 reductase, purified, reconstituted into PtdCho/PtdEtn/PA (2:1:0.06) phospholipid vesicle membranes	<i>trans</i> (+)-B[a]P-7,8-dihydrodiol	<i>trans</i> -(<i>anti</i>)-7,8-Dihydroxy-9,10-epoxy-7,8,9,10-tetrahydro-formation (<i>trans</i> -diol epoxide or DE2 formation)		6.5±0.9	0.4±0.03				[149]
CYP1A1	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes, +NADPH-P450 reductase, purified, reconstituted into Ole2PtdCho/Ole2PtdEtn (2:1) phospholipid vesicle membranes	<i>trans</i> (+)-B[a]P-7,8-dihydrodiol	trans-(anti)-7,8-Dihydroxy-9,10-epoxy-7,8,9,10-tetrahydro-formation (trans-Diolepoxide or DE2 formation)		39.9±8.0	2.2±0.3				[149]
CYP1A1	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes, +NADPH-P450 reductase, purified, reconstituted into Ole2PtdCho/Ela2PtdEtn (2:1) phospholipid vesicle membranes	<i>trans</i> (+)-B[a]P-7,8-dihydrodiol	<i>trans</i> -(<i>anti</i>)-7,8-Dihydroxy-9,10-epoxy-7,8,9,10-tetrahydro-formation (<i>trans</i> -diol epoxide or DE2 formation)		21.9±7.5	0.7±0.2				[149]
CYP1A1	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes, +NADPH-P450 reductase,	<i>trans</i> (+)-B[a]P-7,8-dihydrodiol	<i>cis</i> -(<i>syn</i>)-7,8-Dihydroxy-9,10-epoxy-7,8,9,10-tetrahydro-formation (<i>cis</i> -diol epoxide, or DE1 formation)		7.4±1.4	1.2±0.1				[149]

Enzyme	Model used	Substrate	Reaction	Inhibitor/Ligand	K_m (μ M); (S_{50} (μ M))	V_{max} (nmol/min/nmol of CYP; l/min, or as specified)	Enzyme efficiency (V_{max}/K_m (ml/min/nmol P450, or as specified)	K_i (K_I); (μ M, or as specified)	IC_{50} (μ M, or as specified)	Reference
	purified, reconstituted into Ole2PtdCho phospholipid vesicle membranes									
CYP1A1	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes, +NADPH-P450 reductase, purified, reconstituted into Ole2PtdCho/PtdSer (2:1) phospholipid vesicle membranes	<i>trans</i> -(+)-B[a]P-7,8-dihydrodiol	<i>cis</i> -(<i>syn</i>)-7,8-Dihydroxy-9,10-epoxy-7,8,9,10-tetrahydro-formation (<i>cis</i> -diol epoxide, or DE1 formation)		12.1±3.7	2.8±0.5				[149]
CYP1A1	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes, +NADPH-P450 reductase, purified, reconstituted into Ole2PtdCho/PtdIns (2:1) phospholipid vesicle membranes	<i>trans</i> -(+)-B[a]P-7,8-dihydrodiol	<i>cis</i> -(<i>syn</i>)-7,8-Dihydroxy-9,10-epoxy-7,8,9,10-tetrahydro-formation (<i>cis</i> -diol epoxide, or DE1 formation)		3.7±0.7	1.3±0.08				[149]
CYP1A1	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes, +NADPH-P450 reductase, purified, reconstituted into PtdCho/PtdEtn/PA (2:1:0.06) phospholipid vesicle membranes	<i>trans</i> -(+)-B[a]P-7,8-dihydrodiol	<i>cis</i> -(<i>syn</i>)-7,8-Dihydroxy-9,10-epoxy-7,8,9,10-tetrahydro-formation (<i>cis</i> -diol epoxide, or DE1 formation)		3.7±1.2	0.7±0.08				[149]
CYP1A1	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes, +NADPH-P450 reductase, purified, reconstituted into Ole2PtdCho/Ole2PtdEtn (2:1) phospholipid vesicle membranes	<i>trans</i> -(+)-B[a]P-7,8-dihydrodiol	<i>cis</i> -(<i>syn</i>)-7,8-Dihydroxy-9,10-epoxy-7,8,9,10-tetrahydro-formation (<i>cis</i> -diol epoxide, or DE1 formation)		28.9±8.7	6.0±1.2				[149]
CYP1A1	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes, +NADPH-P450 reductase, purified, reconstituted into Ole2PtdCho/Ela2PtdEtn (2:1) phospholipid vesicle membranes	<i>trans</i> -(+)-B[a]P-7,8-dihydrodiol	<i>cis</i> -(<i>syn</i>)-7,8-Dihydroxy-9,10-epoxy-7,8,9,10-tetrahydro-formation (<i>cis</i> -diol epoxide, or DE1 formation)		9.9±1.9	1.2±0.1				[149]
CYP1A1 Ile462	<i>E. coli</i> expressing human CYP, purified, reconstituted, 40 μ M substrate	B[a]P	7,8-Dihydrodiol formation			0.6				[66]
CYP1A1 Ile462	<i>E. coli</i> expressing human CYP, purified, reconstituted, 100 μ M substrate	B[a]P	7,8-Dihydrodiol formation			0.6				[66]
CYP1A1 Ile462	<i>E. coli</i> expressing human CYP, purified, reconstituted, 40 μ M substrate	B[a]P	9,10-Dihydrodiol formation			1.0				[66]
CYP1A1 Ile462	<i>E. coli</i> expressing human CYP, purified, reconstituted, 100 μ M substrate	B[a]P	9,10-Dihydrodiol formation			1.7				[66]
CYP1A1 Val462	<i>E. coli</i> expressing human CYP, purified, reconstituted, 40 μ M substrate	B[a]P	7,8-Dihydrodiol formation			0.2				[66]
CYP1A1 Val462	<i>E. coli</i> expressing human CYP, purified, reconstituted, 100 μ M substrate	B[a]P	7,8-Dihydrodiol formation			0.2				[66]

Enzyme	Model used	Substrate	Reaction	Inhibitor /Ligand	K_m (μ M); (S_{50} (μ M))	V_{max} (k_{cat} (nmol/min/nmol of CYP; l/min, or as specified)	Enzyme efficiency (V_{max}/K_m (ml/min/nmol or as specified)	K_i (K_I); (μ M, or as specified)	IC_{50} (μ M, or as specified)	Reference
CYP1A1 Val462	<i>E. coli</i> expressing human CYP, purified, reconstituted, 40 μ M substrate	B[a]P	9,10-Dihydrodiol formation			0.6				[66]
CYP1A1 Val462	<i>E. coli</i> expressing human CYP, purified, reconstituted, 100 μ M substrate	B[a]P	9,10-Dihydrodiol formation			1.2				[66]
CYP1A1	Yeast cells (<i>Saccharomyces cerevisiae</i>) expressing human CYP, microsomes	<i>trans</i> -($-$)-B[a]P-7,8-diol	Metabolic activation			1100 $\pm$ 120 <i>umu</i> gene expression units/min/nmol				[26]
CYP1A2	Yeast cells (<i>S. cerevisiae</i>) expressing human CYP, microsomes	<i>trans</i> -($-$)-B[a]P-7,8-diol	Metabolic activation			310 $\pm$ 41 <i>umu</i> gene expression units/min/nmol				[26]
CYP1B1	Yeast cells (<i>S. cerevisiae</i>) expressing human CYP, microsomes	<i>trans</i> -($-$)-B[a]P-7,8-diol	Metabolic activation			940 $\pm$ 130 <i>umu</i> gene expression units/min/nmol				[26]
CYP1A1	Yeast cells (<i>S. cerevisiae</i>) expressing human CYP, microsomes	<i>trans</i> -($+$)-B[a]P-7,8-diol	Metabolic activation			630 $\pm$ 77 <i>umu</i> gene expression units/min/nmol				[26]
CYP1A2	Yeast cells (<i>S. cerevisiae</i>) expressing human CYP, microsomes	<i>trans</i> -($+$)-B[a]P-7,8-diol	Metabolic activation			210 $\pm$ 22 <i>umu</i> gene expression units/min/nmol				[26]
CYP1B1	Yeast cells (<i>S. cerevisiae</i>) expressing human CYP, microsomes	<i>trans</i> -($-$)-B[a]P-7,8-diol	Metabolic activation			1260 $\pm$ 180 <i>umu</i> gene expression units/min/nmol				[26]
CYP1A1	Yeast cells (<i>S. cerevisiae</i>) expressing human CYP, microsomes	B[a]P	Oxidation (metabolic activation)			130 $\pm$ 20 <i>umu</i> gene expression units/min/nmol				[26]
CYP1A2	Yeast cells (<i>S. cerevisiae</i>) expressing human CYP, microsomes	B[a]P	Oxidation (metabolic activation)			39 $\pm$ 29 <i>umu</i> gene expression units/min/nmol				[26]
CYP1B1	Yeast cells (<i>S. cerevisiae</i>) expressing human CYP, microsomes	<i>trans</i> -($+$)-B[a]P-4,5-dihydrodiol	Oxidation (metabolic activation)			87 $\pm$ 34 <i>umu</i> gene expression units/min/nmol				[26]
CYP1A1	<i>E. coli</i> expressing human CYP, membranes	($+$)-B[a]P-7,8-diol	Metabolic activation		1.9	2090 (<i>umu</i> gene expression units/min/nmol)				[30]

Enzyme	Model used	Substrate	Reaction	K_m (μ M); (S_{50} (μ M))	V_{max} (nmol/min/nmol of CYP; l/min, or as specified)	Enzyme efficiency (V_{max}/K_m (ml/min/nmol P450, or as specified)	K_i (μ M); or as specified)	IC_{50} (μ M, or as specified)	Reference
CYP1B1.1	<i>Salmonella typhimurium</i> expressing human CYP, microsomes	(+,-)-B[a]P-7,8-diol	Metabolic activation	1.4	1290 (<i>umu</i> gene expression units/min/nmol)				[30]
CYP1B1.2	<i>S. typhimurium</i> expressing human CYP, microsomes	(+,-)-B[a]P-7,8-diol	Metabolic activation	1.9	1390 (<i>umu</i> gene expression units/min/nmol)				[30]
CYP1B1.3	<i>S. typhimurium</i> expressing human CYP, microsomes	(+,-)-B[a]P-7,8-diol	Metabolic activation	2.6	2270 (<i>umu</i> gene expression units/min/nmol)				[30]
CYP1B1.6	<i>S. typhimurium</i> expressing human CYP, microsomes	(+,-)-B[a]P-7,8-diol	Metabolic activation	2.2	1940 (<i>umu</i> gene expression units/min/nmol)				[30]
CYP1A1	<i>E. coli</i> expressing human CYP, membranes	B[a]P	Metabolic activation	7.3	150 (<i>umu</i> gene expression units/min/nmol)				[30]
CYP1B1.1	<i>S. typhimurium</i> expressing human CYP, microsomes	B[a]P	Metabolic activation	5.1	160 (<i>umu</i> gene expression units/min/nmol)				[30]
CYP1B1.2	<i>S. typhimurium</i> expressing human CYP, microsomes	B[a]P	Metabolic activation	7.4	440 (<i>umu</i> gene expression units/min/nmol)				[30]
CYP1B1.3	<i>S. typhimurium</i> expressing human CYP, microsomes	B[a]P	Metabolic activation	3.8	450 (<i>umu</i> gene expression units/min/nmol)				[30]
CYP1B1.6	<i>S. typhimurium</i> expressing human CYP, microsomes	B[a]P	Metabolic activation	5.5	220 (<i>umu</i> gene expression units/min/nmol)				[30]
CYP1A1	<i>E. coli</i> expressing human CYP, purified	B[a]P	C3-Hydroxylation,		0.929				[33]
CYP1A2	<i>E. coli</i> expressing human CYP, purified	B[a]P	C3-Hydroxylation,		0.023				[33]
CYP1B1	Yeast cells (<i>S. cerevisiae</i>) expressing human CYP, microsomes	B[a]P	C3-Hydroxylation,		0.42				[33]
CYP3A4	<i>E. coli</i> expressing human CYP, purified	B[a]P	C3-Hydroxylation,		0.038				[33]
CYP1A1	<i>E. coli</i> expressing human CYP, purified	B[a]P	Dihydrodiol 4,5-formation		0.11				53

Enzyme	Model used	Substrate	Reaction	K_m (μ M); (S_{50} (μ M))	V_{max} (nmol/min/nmol of CYP; l/min, or as specified)	Enzyme efficiency (V_{max}/K_m (ml/min/nmol P450, or as specified)	K_i (K_I); (μ M, or as specified)	IC_{50} (μ M, or as specified)	Reference
CYP1A1	<i>E. coli</i> expressing human CYP, purified, + α -naphthoflavone	B[a]P	Dihydrodiol 4,5-formation		0.1				53
CYP1A1	<i>E. coli</i> expressing human CYP, purified	B[a]P	Dihydrodiol 7,8-formation		0.59				53
CYP1A1	<i>E. coli</i> expressing human CYP, purified, + α -naphthoflavone	B[a]P	Dihydrodiol 7,8-formation		0.51				[53]
CYP1A1	<i>E. coli</i> expressing human CYP, purified	B[a]P	Dihydrodiol 9,10-formation		0.50				[53]
CYP1A1	<i>E. coli</i> expressing human CYP, purified, + α -naphthoflavone	B[a]P	Dihydrodiol 9,10-formation		1100				[53]
CYP1A1	<i>E. coli</i> expressing human CYP, purified	B[a]P	C3-Hydroxylation,		0.71				[53]
CYP1A1	<i>E. coli</i> expressing human CYP, purified, + α -naphthoflavone	B[a]P	Hydroxylation, C3-		0.45				[53]
CYP1A1	<i>E. coli</i> expressing human CYP, purified	B[a]P	C9-Hydroxylation,		0.06				[53]
CYP1A1	<i>E. coli</i> expressing human CYP, purified, + α -naphthoflavone	B[a]P	C9-Hydroxylation,		0.02				[53]
CYP1A1	<i>E. coli</i> expressing human CYP, purified	B[a]P	Quinone formation		0.11				[53]
CYP1A1	<i>E. coli</i> expressing human CYP, purified, + α -naphthoflavone	B[a]P	Quinone formation		0.092				[53]
CYP1A2	<i>E. coli</i> expressing human CYP, purified	B[a]P	4,5-Dihydrodiol formation		0.104				[53]
CYP1A2	<i>E. coli</i> expressing human CYP, purified, + α -naphthoflavone	B[a]P	4,5-Dihydrodiol formation		0.054				[53]
CYP1A2	<i>E. coli</i> expressing human CYP, purified	B[a]P	4,5-Dihydrodiol formation		0.026				[53]
CYP1A2	<i>E. coli</i> expressing human CYP, purified	B[a]P	4,5-Dihydrodiol formation		0.023				[53]
CYP1A2	<i>E. coli</i> expressing human CYP, purified	B[a]P	C3-Hydroxylation,		0.164				[53]
CYP1A2	<i>E. coli</i> expressing human CYP, purified, + α -naphthoflavone	B[a]P	C3-Hydroxylation,		0.001				[53]
CYP1A2	<i>E. coli</i> expressing human CYP, purified	B[a]P	C9-Hydroxylation,		0.02				[53]
CYP1A2	<i>E. coli</i> expressing human CYP, purified	B[a]P	Quinone formation		0.044				[53]
CYP2C18	<i>E. coli</i> expressing human CYP, purified	B[a]P	7,8-Dihydrodiol formation		0.001				[53]

Enzyme	Model used	Substrate	Reaction	K_m (μ M); (S_{50} (μ M))	V_{max} (nmol/min/nmol of CYP; l/min, or as specified)	Enzyme efficiency V_{max}/K_m (ml/min/nmol P450, or as specified)	K_i (K_I); (μ M, or as specified)	IC_{50} (μ M, or as specified)	Reference
CYP2C18	<i>E. coli</i> expressing human CYP, purified	B[a]P	C3-Hydroxylation		0.022				[53]
CYP2C8	<i>E. coli</i> expressing human CYP, purified	B[a]P	4,5-Dihydrodiol formation		0.015				[53]
CYP2C8	<i>E. coli</i> expressing human CYP, purified	B[a]P	7,8-Dihydrodiol formation		0.005				[53]
CYP2C8	<i>E. coli</i> expressing human CYP, purified	B[a]P	C3-Hydroxylation		0.005				[53]
CYP2C9	<i>E. coli</i> expressing human CYP, purified	B[a]P	7,8-Dihydrodiol formation		0.002				[53]
CYP2C9	<i>E. coli</i> expressing human CYP, purified	B[a]P	C3-Hydroxylation		0.011				[53]
CYP2E1	<i>E. coli</i> expressing human CYP, purified, + <i>b</i> ₅	B[a]P	7,8-Dihydrodiol formation		0.002				[53]
CYP2E1	<i>E. coli</i> expressing human CYP, purified, + <i>b</i> ₅	B[a]P	C3-Hydroxylation,		0.017				[53]
CYP2E1	<i>E. coli</i> expressing human CYP, purified, + <i>b</i> ₅	B[a]P	C9-Hydroxylation,		0.001				[53]
CYP3A4	<i>E. coli</i> expressing human CYP, purified, + <i>b</i> ₅	B[a]P	4,5-Dihydrodiol formation		0.023				[53]
CYP3A4	<i>E. coli</i> expressing human CYP, purified, + <i>b</i> ₅ , GSH	B[a]P	4,5-Dihydrodiol formation		0.035				[53]
CYP3A4	<i>E. coli</i> expressing human CYP, purified, + <i>b</i> ₅	B[a]P	7,8-Dihydrodiol formation		0.003				[53]
CYP3A4	<i>E. coli</i> expressing human CYP, purified, + <i>b</i> ₅	B[a]P	9,10-Dihydrodiol formation		0.012				[53]
CYP3A4	<i>E. coli</i> expressing human CYP, purified, + <i>b</i> ₅ , GSH	B[a]P	9,10-Dihydrodiol formation		0.02				[53]
CYP3A4	<i>E. coli</i> expressing human CYP, purified, + <i>b</i> ₅	B[a]P	C3-Hydroxylation,		0.24				[53]
CYP3A4	<i>E. coli</i> expressing human CYP, purified, + <i>b</i> ₅ , GSH	B[a]P	C3-Hydroxylation,		0.24				[53]
CYP3A4	<i>E. coli</i> expressing human CYP, purified, + <i>b</i> ₅	B[a]P	C9-Hydroxylation,		0.007				[53]
CYP3A4	<i>E. coli</i> expressing human CYP, purified, + <i>b</i> ₅ , GSH	B[a]P	C9-Hydroxylation,		0.005				[53]
CYP3A4	<i>E. coli</i> expressing human CYP, purified, + <i>b</i> ₅	B[a]P	Quinone formation		0.017				[53]
CYP3A4	<i>E. coli</i> expressing human CYP, purified, + <i>b</i> ₅ , GSH	B[a]P	Quinone formation		0.029				[53]
CYP1A1.1	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes	B[a]P	B[a]P-1,6-dione formation		0.14				[57]
CYP1A1.1	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes, +epoxide hydrolase	B[a]P	B[a]P-1,6-dione formation		0.18				[57]

Enzyme	Model used	Substrate	Reaction	K_m (μ M); (S_{50} (μ M))	V_{max} (k_{cat} (nmol/min/nmol of CYP; l/min, or as specified)	Enzyme efficiency (V_{max}/K_m (ml/min/nmol P450, or as specified)	K_i (K_I); (μ M, or as specified)	IC_{50} (μ M, or as specified)	Reference
CYP1A1.1	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes	B[a]P	B[a]P-3,6-dione formation		0.39				[57]
CYP1A1.1	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes, +epoxide hydrolase	B[a]P	B[a]P-3,6-dione formation		0.39				[57]
CYP1A1.1	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes	B[a]P	B[a]P-6,12-dione formation		0.39				[57]
CYP1A1.1	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes, +epoxide hydrolase	B[a]P	B[a]P-6,12-dione formation		0.4				[57]
CYP1A1.1	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes, +epoxide hydrolase	B[a]P	B[a]P- <i>trans</i> -4,5-dihydrodiol formation		0.05				[57]
CYP1A1.1	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes	B[a]P	B[a]P- <i>trans</i> -7,8-dihydrodiol formation		0.41				[57]
CYP1A1.1	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes, +epoxide hydrolase	B[a]P	B[a]P- <i>trans</i> -7,8-dihydrodiol formation		0.42				[57]
CYP1A1.1	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes	B[a]P	B[a]P- <i>trans</i> -7,8-dihydrodiol formation		13.8±1.6	1.1±0.2			[57]
CYP1A1.1	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes, +epoxide hydrolase	B[a]P	B[a]P- <i>trans</i> -7,8-dihydrodiol formation		8.8±0.9	1.1±0.3			[57]
CYP1A1.1	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes	B[a]P	B[a]P- <i>trans</i> -9,10-dihydrodiol formation		0.1				[57]
CYP1A1.1	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes, +epoxide hydrolase	B[a]P	B[a]P- <i>trans</i> -9,10-dihydrodiol formation		0.41				[57]
CYP1A1.1	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes	B[a]P	B[a]P- <i>trans</i> -9,10-dihydrodiol formation		1.8±0.7	0.1±0.1			[57]
CYP1A1.1	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes, +epoxide hydrolase	B[a]P	B[a]P- <i>trans</i> -9,10-dihydrodiol formation		4.7±0.5	0.8±0.1			[57]
CYP1A1.1	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes	B[a]P	C3-Hydroxylation,		1.14				[57]
CYP1A1.1	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes, +epoxide hydrolase	B[a]P	C3-Hydroxylation,		0.99				[57]
CYP1A1.1	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes	B[a]P	C3-Hydroxylation,		8.2±0.9	2.1±0.1			[57]

Enzyme	Model used	Substrate	Reaction	Inhibitor/Ligand	K_m (μ M); (S_{50} (μ M))	V_{max} (nmol/min/nmol of CYP; l/min, or as specified)	Enzyme efficiency (V_{max}/K_m (ml/nmol P450, or as specified)	K_i (μ M); or as specified)	IC_{50} (μ M, or as specified)	Reference
CYP1A1.1	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes, +epoxide hydrolase	B[a]P	C3-Hydroxylation,		6.9±0.9	2.1±0.2				[57]
CYP1A1.1	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes	B[a]P	C9-Hydroxylation,			0.73				[57]
CYP1A1.1	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes, +epoxide hydrolase	B[a]P	C9-Hydroxylation,			0.51				[57]
CYP1A1.1	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes	B[a]P	C9-Hydroxylation,		9.5±1.3	1.6±0.2				[57]
CYP1A1.1	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes, +epoxide hydrolase	B[a]P	C9-Hydroxylation,		10.4±1.3	1.1±0.1				[57]
CYP1A1.2	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes, +epoxide hydrolase	B[a]P	B[a]P-1,6-dione formation			0.01				[57]
CYP1A1.2	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes	B[a]P	B[a]P-3,6-dione formation			0.17				[57]
CYP1A1.2	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes, +epoxide hydrolase	B[a]P	B[a]P-3,6-dione formation			0.18				[57]
CYP1A1.2	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes	B[a]P	B[a]P-6,12-dione formation			0.25				[57]
CYP1A1.2	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes, +epoxide hydrolase	B[a]P	B[a]P-6,12-dione formation			0.23				[57]
CYP1A1.2	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes, +epoxide hydrolase	B[a]P	B[a]P- <i>trans</i> -4,5-dihydrodiol formation			0.02				[57]
CYP1A1.2	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes	B[a]P	B[a]P- <i>trans</i> -7,8-dihydrodiol formation			0.18				[57]
CYP1A1.2	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes, +epoxide hydrolase	B[a]P	B[a]P- <i>trans</i> -7,8-dihydrodiol formation			0.23				[57]
CYP1A1.2	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes	B[a]P	B[a]P- <i>trans</i> -7,8-dihydrodiol formation		3.5±0.8	0.2±0.1				[57]
CYP1A1.2	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes, +epoxide hydrolase	B[a]P	B[a]P- <i>trans</i> -7,8-dihydrodiol formation		3.6±0.8	0.3±0.1				[57]
CYP1A1.2	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes	B[a]P	B[a]P- <i>trans</i> -9,10-dihydrodiol formation			0.1				[57]

Enzyme	Model used	Substrate	Reaction	Inhibitor/Ligand	K_m (μM); (S_{50} (μM))	V_{max} (k_{cat} (nmol/min/nmol of CYP; V_{max}/K_m (ml/min, or as specified)	Enzyme efficiency (K_i (μM); or as specified)	IC_{50} (μM , or as specified)	Reference
CYP1A1.2	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes, +epoxide hydrolase	B[a]P	B[a]P- <i>trans</i> -9,10-dihydrodiol formation			0.23			[57]
CYP1A1.2	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes	B[a]P	B[a]P- <i>trans</i> -9,10-dihydrodiol formation		1.3±0.6	0.1±0.1			[57]
CYP1A1.2	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes, +epoxide hydrolase	B[a]P	B[a]P- <i>trans</i> -9,10-dihydrodiol formation		1.9±0.7	0.3±0.1			[57]
CYP1A1.2	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes	B[a]P	C3-Hydroxylation,			0.6			[57]
CYP1A1.2	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes, +epoxide hydrolase	B[a]P	C3-Hydroxylation,			0.65			[57]
CYP1A1.2	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes	B[a]P	C3-Hydroxylation,		1.9±0.7	0.7±0.1			[57]
CYP1A1.2	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes, +epoxide hydrolase	B[a]P	C3-Hydroxylation,		1.7±0.7	0.6±0.1			[57]
CYP1A1.2	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes	B[a]P	C9-Hydroxylation,			0.25			[57]
CYP1A1.2	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes, +epoxide hydrolase	B[a]P	C9-Hydroxylation,			0.21			[57]
CYP1A1.2	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes	B[a]P	C9-Hydroxylation,		4.0±1.0	0.6±0.1			[57]
CYP1A1.2	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes, +epoxide hydrolase	B[a]P	C9-Hydroxylation,		4.5±1.1	0.4±0.1			[57]
CYP1A1.4	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes	B[a]P	B[a]P-1,6-dione formation			0.12			[57]
CYP1A1.4	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes, +epoxide hydrolase	B[a]P	B[a]P-1,6-dione formation			0.06			[57]
CYP1A1.4	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes	B[a]P	B[a]P-3,6-dione formation			0.3			[57]
CYP1A1.4	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes, +epoxide hydrolase	B[a]P	B[a]P-3,6-dione formation			0.29			[57]
CYP1A1.4	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes	B[a]P	B[a]P-6,12-dione formation			0.3			[57]

Enzyme	Model used	Substrate	Reaction	Inhibitor/Ligand	K_m (μ M); (S_{50} (μ M))	V_{max} (k_{cat} (nmol/min/nmol of CYP; l/min , or as specified)	Enzyme efficiency (V_{max}/K_m (ml/min/nmol P450, or as specified)	K_i (K_I); (μ M, or as specified)	IC_{50} (μ M, or as specified)	Reference
CYP1A1.4	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes, +epoxide hydrolase	B[a]P	B[a]P-6,12-dione formation			0.24				[57]
CYP1A1.4	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes	B[a]P	B[a]P- <i>trans</i> -4,5-dihydrodiol formation			0.02				[57]
CYP1A1.4	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes, +epoxide hydrolase	B[a]P	B[a]P- <i>trans</i> -4,5-dihydrodiol formation			0.05				[57]
CYP1A1.4	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes	B[a]P	B[a]P- <i>trans</i> -7,8-dihydrodiol formation			0.36				[57]
CYP1A1.4	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes, +epoxide hydrolase	B[a]P	B[a]P- <i>trans</i> -7,8-dihydrodiol formation			0.35				[57]
CYP1A1.4	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes	B[a]P	B[a]P- <i>trans</i> -7,8-dihydrodiol formation		7.7±0.9	0.5±0.1				[57]
CYP1A1.4	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes, +epoxide hydrolase	B[a]P	B[a]P- <i>trans</i> -7,8-dihydrodiol formation		9.4±1.0	0.6±0.1				[57]
CYP1A1.4	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes	B[a]P	B[a]P- <i>trans</i> -9,10-dihydrodiol formation			0.12				[57]
CYP1A1.4	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes, +epoxide hydrolase	B[a]P	B[a]P- <i>trans</i> -9,10-dihydrodiol formation			0.42				[57]
CYP1A1.4	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes	B[a]P	B[a]P- <i>trans</i> -9,10-dihydrodiol formation		1.5±0.4	0.1±0.1				[57]
CYP1A1.4	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes, +epoxide hydrolase	B[a]P	B[a]P- <i>trans</i> -9,10-dihydrodiol formation		2.5±0.8	0.5±0.1				[57]
CYP1A1.4	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes	B[a]P	C3-Hydroxylation			0.65				[57]
CYP1A1.4	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes, +epoxide hydrolase	B[a]P	C3-Hydroxylation			0.75				[57]
CYP1A1.4	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes	B[a]P	C3-Hydroxylation		8.9±0.9	1.3±0.2				[57]
CYP1A1.4	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes, +epoxide hydrolase	B[a]P	C3-Hydroxylation		6.5±0.8	1.1±0.2				[57]
CYP1A1.4	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes	B[a]P	C9-Hydroxylation			0.46				[57]

Enzyme	Model used	Substrate	Reaction	Inhibitor/Ligand	K_m (μM); (S_{50} (μM))	V_{max} (k_{cat} (nmol/min/nmol CYP; l/min, or as specified)	Enzyme efficiency (V_{max}/K_m (ml/min/nmol P450, or as specified)	K_i (μM); or as specified)	IC_{50} (μM , or as specified)	Reference
CYP1A1.4	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes, +epoxide hydrolase	B[a]P	C9-Hydroxylation			0.33				[57]
CYP1A1.4	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes	B[a]P	C9-Hydroxylation		8.5±1.0	0.8±0.1				[57]
CYP1A1.4	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes, +epoxide hydrolase	B[a]P	C9-Hydroxylation		5.5±0.8	0.4±0.1				[57]
CYP1A1.1	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes	<i>trans</i> -(−)-B[a]P-7,8-diol	<i>anti</i> -7,8-Dihydroxy-9,10-epoxy-7,8,9,10-tetrahydro-formation (diol epoxide formation)			7.4±0.9				[57]
CYP1A1.1	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes	<i>trans</i> -(−)-B[a]P-7,8-diol	<i>anti</i> -7,8-Dihydroxy-9,10-epoxy-7,8,9,10-tetrahydro-formation (diol epoxide formation)			7.8±0.9				[57]
CYP1A1.1	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes	<i>trans</i> -(−)-B[a]P-7,8-diol	<i>anti</i> -7,8-Dihydroxy-9,10-epoxy-7,8,9,10-tetrahydro-formation (diol epoxide formation)			8.2±0.8				[57]
CYP1A1.1	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes	<i>trans</i> -(−)-B[a]P-7,8-diol	<i>syn</i> -7,8-Dihydroxy-9,10-epoxy-7,8,9,10-tetrahydro-formation (diol epoxide formation)			2.6±0.4				[57]
CYP1A1.1	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes	<i>trans</i> -(−)-B[a]P-7,8-diol	<i>syn</i> -7,8-Dihydroxy-9,10-epoxy-7,8,9,10-tetrahydro-formation (diol epoxide formation)			2.5±0.4				[57]
CYP1A1.1	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes	<i>trans</i> -(−)-B[a]P-7,8-diol	<i>syn</i> -7,8-Dihydroxy-9,10-epoxy-7,8,9,10-tetrahydro-formation (diol epoxide formation)			2.8±0.3				[57]
CYP1A1.2	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes	<i>trans</i> -(−)-B[a]P-7,8-diol	<i>anti</i> -7,8-Dihydroxy-9,10-epoxy-7,8,9,10-tetrahydro-formation (diol epoxide formation)			5.1±0.7				[57]
CYP1A1.2	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes	<i>trans</i> -(−)-B[a]P-7,8-diol	<i>anti</i> -7,8-Dihydroxy-9,10-epoxy-7,8,9,10-tetrahydro-formation (diol epoxide formation)			5.5±0.7				[57]
CYP1A1.2	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes	<i>trans</i> -(−)-B[a]P-7,8-diol	<i>anti</i> -7,8-Dihydroxy-9,10-epoxy-7,8,9,10-tetrahydro-formation (diol epoxide formation)			6.1±0.6				[57]
CYP1A1.2	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes	<i>trans</i> -(−)-B[a]P-7,8-diol	<i>syn</i> -7,8-Dihydroxy-9,10-epoxy-7,8,9,10-tetrahydro-formation (diol epoxide formation)			1.6±0.3				[57]
CYP1A1.2	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes	<i>trans</i> -(−)-B[a]P-7,8-diol	<i>syn</i> -7,8-Dihydroxy-9,10-epoxy-7,8,9,10-tetrahydro-formation (diol epoxide formation)			1.6±0.3				[57]
CYP1A1.2	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes	<i>trans</i> -(−)-B[a]P-7,8-diol	<i>syn</i> -7,8-Dihydroxy-9,10-epoxy-7,8,9,10-tetrahydro-formation (diol epoxide formation)			1.75±0.2				[57]
CYP1A1.4	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes	<i>trans</i> -(−)-B[a]P-7,8-diol	<i>anti</i> -7,8-Dihydroxy-9,10-epoxy-7,8,9,10-tetrahydro-formation (diol epoxide formation)			3.9±0.6				[57]

Enzyme	Model used	Substrate	Reaction	Inhibitor /Ligand	K_m (μ M); (S_{50} (μ M))	V_{max} (k_{cat} (nmol/min/nmol CYP; l/min, or as specified)	Enzyme efficiency (V_{max}/K_m (ml/min/nmol P450, or as specified)	K_i (K_I); (μ M, or as specified)	IC_{50} (μ M, or as specified)	Reference
CYP1A1.4	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes	<i>trans</i> (-)-B[a]P-7,8-diol	<i>anti</i> -7,8-Dihydroxy-9,10-epoxy-7,8,9,10-tetrahydro-formation (diol epoxide formation)			4.1±0.6				[57]
CYP1A1.4	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes	<i>trans</i> (-)-B[a]P-7,8-diol	<i>anti</i> -7,8-Dihydroxy-9,10-epoxy-7,8,9,10-tetrahydro-formation (diol epoxide formation)			4.6±0.5				[57]
CYP1A1.4	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes	<i>trans</i> (-)-B[a]P-7,8-diol	<i>syn</i> -7,8-Dihydroxy-9,10-epoxy-7,8,9,10-tetrahydro-formation (diol epoxide formation)			1.2±0.2				[57]
CYP1A1.4	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes	<i>trans</i> (-)-B[a]P-7,8-diol	<i>syn</i> -7,8-Dihydroxy-9,10-epoxy-7,8,9,10-tetrahydro-formation (diol epoxide formation)			1.2±0.2				[57]
CYP1A1.4	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes	<i>trans</i> (-)-B[a]P-7,8-diol	<i>syn</i> -7,8-Dihydroxy-9,10-epoxy-7,8,9,10-tetrahydro-formation (diol epoxide formation)			1.3±0.2				[57]
CYP3A4	Yeast cells expressing human CYP, microsomes	B[a]P	Hydroxylation	Diclobutazol (<i>R,R</i>)-					0.75±0.1[150]	
CYP3A4	Yeast cells expressing human CYP, microsomes	B[a]P	Hydroxylation	Diclobutazol (<i>S,S</i>)-					1.50±0.1[850]	
CYP3A4	Yeast cells expressing human CYP, microsomes	B[a]P	Hydroxylation	Diclobutazol					1.00±0.1[550]	
CYP3A4	Yeast cells expressing human CYP, microsomes	B[a]P	Hydroxylation	Itraconazole					0.2±0.1 [150]	
CYP3A4	Yeast cells expressing human CYP, microsomes	B[a]P	Hydroxylation	Ketoconazole					0.25±0.0[150]	
CYP3A4	Yeast cells expressing human CYP, microsomes	B[a]P	Hydroxylation	SCH39304 (<i>R,R</i>)-(+)					1.50±0.4[550]	
CYP3A4	Yeast cells expressing human CYP, microsomes	B[a]P	Hydroxylation	SCH39304 racemate					4.00±0.8[550]	
CYP1A1	Baculovirus-infected insect cells expressing human CYP (Supersomes®), microsomes, 40 μ M substrate	B[a]P	C1-Hydroxylation			1.45				[60]
CYP1A1	Baculovirus-infected insect cells expressing human CYP (Supersomes®), microsomes, 40 μ M substrate	B[a]P	C3-Hydroxylation			1.46				[60]
CYP1A1	Baculovirus-infected insect cells expressing human CYP (Supersomes®), microsomes, 40 μ M substrate	B[a]P	C9-Hydroxylation			0.6				[60]
CYP1A1	Baculovirus-infected Sf9 insect cells expressing human CYP, purified, reconstituted, 5 μ M substrate	B[a]P	3-Hydroxylation	Apigenin					48±4	[60]
CYP1A1	Baculovirus-infected Sf9 insect cells expressing human CYP, purified, reconstituted, 5 μ M substrate	B[a]P	3-Hydroxylation	Myricetin					40±4	[59]
CYP1A1	Baculovirus-infected Sf9 insect cells expressing human CYP, purified, reconstituted, 5 μ M substrate	B[a]P	3-Hydroxylation	(-)-Epigallocatechin-3-gallate, EGCG					51±6	[59]

Enzyme	Model used	Substrate	Reaction	K_m (μ M); (S_{50} (μ M))	V_{max} (k_{cat} (nmol/min/nmol CYP; l/min, or as specified)	Enzyme efficiency (V_{max}/K_m (ml/min/nmol P450, or as specified)	K_i (μ M); or as specified)	IC_{50} (μ M, or as specified)	Reference
CYP1A1	Baculovirus-infected Sf9 insect cells expressing human CYP, purified, reconstituted, 2 μ M substrate	<i>trans</i> -(−)-B[a]P-7,8-diol	<i>trans</i> -7,8-Dihydroxy-9,10-epoxy-7,8,9,10-tetrahydro-formation (diol epoxide formation)					1.5±0.2 [59]	
CYP1A1	Baculovirus-infected Sf9 insect cells expressing human CYP, purified, reconstituted, 2 μ M substrate	<i>trans</i> -(−)-B[a]P-7,8-diol	<i>trans</i> -7,8-Dihydroxy-9,10-epoxy-7,8,9,10-tetrahydro-formation (diol epoxide formation)					1.0±0.2 [59]	
CYP1A1	Baculovirus-infected Sf9 insect cells expressing human CYP, purified, reconstituted, 2 μ M substrate	<i>trans</i> -(−)-B[a]P-7,8-diol	<i>trans</i> -7,8-Dihydroxy-9,10-epoxy-7,8,9,10-tetrahydro-formation (Diol epoxide formation)					1.5±0.2 [59]	
CYP1A1	Baculovirus-infected Sf9 insect cells expressing human CYP, purified, reconstituted, 2 μ M substrate	<i>trans</i> -(−)-B[a]P-7,8-diol	<i>trans</i> -7,8-Dihydroxy-9,10-epoxy-7,8,9,10-tetrahydro-formation (diol epoxide formation)					5.2±0.4 [59]	
CYP1A1	Baculovirus-infected Sf9 insect cells expressing human CYP, purified, reconstituted, 2 μ M substrate	<i>trans</i> -(−)-B[a]P-7,8-diol	<i>trans</i> -7,8-Dihydroxy-9,10-epoxy-7,8,9,10-tetrahydro-formation (diol epoxide formation)					10.5±1.5 [59]	
CYP1A1	Baculovirus-infected Sf9 insect cells expressing human CYP, purified, reconstituted, 2 μ M substrate	<i>trans</i> -(−)-B[a]P-7,8-diol	<i>trans</i> -7,8-Dihydroxy-9,10-epoxy-7,8,9,10-tetrahydro-formation (diol epoxide formation)				(−)-Epigallocatechin-3-gallate, EGCG	4.0±0.4 [59]	
CYP1B1*3 (RAVN); Arg48, Ala119, Val432, Ser453	Yeast cells (<i>S. cerevisiae</i>) expressing human CYP, microsomes	<i>trans</i> -(−)-B[a]P-7,8-diol	<i>trans</i> -(<i>anti</i>)-7,8-Dihydroxy-9,10-epoxy-7,8,9,10-tetrahydro-formation (<i>trans</i> -diol epoxide formation) and tetrol (RTTC) formation	4.7±1.1	1.1±0.1	0.24			[151]
CYP1B1 RAVS; Arg48, Ala119, Val432, Ser453	Yeast cells (<i>S. cerevisiae</i>) expressing human CYP, microsomes	<i>trans</i> -(−)-B[a]P-7,8-diol	<i>trans</i> -(<i>anti</i>)-7,8-Dihydroxy-9,10-epoxy-7,8,9,10-tetrahydro-formation (<i>trans</i> -diol epoxide formation) and tetrol (RTTC) formation	1.08±0.26	1.35±0.08	1.25			[151]
CYP1B1 RALN	Yeast cells (<i>S. cerevisiae</i>) expressing human CYP, microsomes	<i>trans</i> -(−)-B[a]P-7,8-diol	<i>trans</i> -(<i>anti</i>)-7,8-Dihydroxy-9,10-epoxy-7,8,9,10-tetrahydro-formation (<i>trans</i> -diol epoxide formation) and tetrol (RTTC) formation	1.84±0.25	1.02±0.04	0.55			[151]
CYP1B1*4 (RALS); Arg48, Ala119, Leu432, Ser453	Yeast cells (<i>S. cerevisiae</i>) expressing human CYP, microsomes	<i>trans</i> -(−)-B[a]P-7,8-diol	<i>trans</i> -(<i>anti</i>)-7,8-Dihydroxy-9,10-epoxy-7,8,9,10-tetrahydro-formation (<i>trans</i> -diol epoxide formation) and tetrol (RTTC) formation	0.76±0.20	0.44±0.03	0.58			[151]
CYP1B1*6 (GSVN)	Yeast cells (<i>S. cerevisiae</i>) expressing human CYP, microsomes	<i>trans</i> -(−)-B[a]P-7,8-diol	<i>trans</i> -(<i>anti</i>)-7,8-Dihydroxy-9,10-epoxy-7,8,9,10-tetrahydro-formation (<i>trans</i> -diol epoxide formation) and tetrol (RTTC) formation	2.9±0.5	0.72±0.05	0.26			[151]
CYP1B1 GSVS	Yeast cells (<i>S. cerevisiae</i>) expressing human CYP, microsomes	<i>trans</i> -(−)-B[a]P-7,8-diol	<i>trans</i> -(<i>anti</i>)-7,8-Dihydroxy-9,10-epoxy-7,8,9,10-tetrahydro-formation (<i>trans</i> -diol epoxide formation) and tetrol (RTTC) formation	2.6±0.4	1.00±0.06	0.39			[151]
CYP1B1*2 (GSLN)	Yeast cells (<i>S. cerevisiae</i>) expressing human CYP, microsomes	<i>trans</i> -(−)-B[a]P-7,8-diol	<i>trans</i> -(<i>anti</i>)-7,8-Dihydroxy-9,10-epoxy-7,8,9,10-tetrahydro-formation (<i>trans</i> -diol epoxide formation) and tetrol (RTTC) formation	1.71±0.49	0.64±0.06	0.37			[151]
CYP1B1 GSLS	Yeast cells (<i>S. cerevisiae</i>) expressing human CYP, microsomes	<i>trans</i> -(−)-B[a]P-7,8-diol	<i>trans</i> -(<i>anti</i>)-7,8-Dihydroxy-9,10-epoxy-7,8,9,10-tetrahydro-formation (<i>trans</i> -diol epoxide formation) and tetrol (RTTC) formation	2.08±0.75	0.84±0.12	0.4			[151]

Enzyme	Model used	Substrate	Reaction	K_m (μ M); (S_{50} (μ M))	V_{max} (k_{cat} (nmol/min/nmol CYP; k_m l/min, or as specified)	Enzyme efficiency (V_{max}/K_m (ml/min/nmol P450, or as specified)	K_i (μ M); or as specified)	IC_{50} (μ M); or as specified)	Reference
CYP1B1 RSVN	Yeast cells (<i>S. cerevisiae</i>) expressing human CYP, microsomes	<i>trans</i> -(−)-B[a]P-7,8-diol	<i>trans</i> -(<i>anti</i>)-7,8-Dihydroxy-9,10-epoxy-7,8,9,10-tetrahydro-formation (trans-diol epoxide formation) and tetrol (RTTC) formation	0.76±0.20	0.94±0.05	1.23			[151]
CYP1B1 RSVS	Yeast cells (<i>S. cerevisiae</i>) expressing human CYP, microsomes	<i>trans</i> -(−)-B[a]P-7,8-diol	<i>trans</i> -(<i>anti</i>)-7,8-Dihydroxy-9,10-epoxy-7,8,9,10-tetrahydro-formation (trans-diol epoxide formation) and tetrol (RTTC) formation	1.04±0.31	0.66±0.05	0.64			[151]
CYP1B1 RSLN	Yeast cells (<i>S. cerevisiae</i>) expressing human CYP, microsomes	<i>trans</i> -(−)-B[a]P-7,8-diol	<i>trans</i> -(<i>anti</i>)-7,8-Dihydroxy-9,10-epoxy-7,8,9,10-tetrahydro-formation (trans-diol epoxide formation) and tetrol (RTTC) formation	1.73±0.24	0.69±0.03	0.4			[151]
CYP1B1 RSLS	Yeast cells (<i>S. cerevisiae</i>) expressing human CYP, microsomes	<i>trans</i> -(−)-B[a]P-7,8-diol	<i>trans</i> -(<i>anti</i>)-7,8-Dihydroxy-9,10-epoxy-7,8,9,10-tetrahydro-formation (trans-diol epoxide formation) and tetrol (RTTC) formation	1.94±0.40	0.78±0.06	0.4			[151]
CYP1B1 GAVN	Yeast cells (<i>S. cerevisiae</i>) expressing human CYP, microsomes	<i>trans</i> -(−)-B[a]P-7,8-diol	<i>trans</i> -(<i>anti</i>)-7,8-Dihydroxy-9,10-epoxy-7,8,9,10-tetrahydro-formation (trans-diol epoxide formation) and tetrol (RTTC) formation	0.86±0.25	0.68±0.04	0.79			[151]
CYP1B1 GAVS	Yeast cells (<i>S. cerevisiae</i>) expressing human CYP, microsomes	<i>trans</i> -(−)-B[a]P-7,8-diol	<i>trans</i> -(<i>anti</i>)-7,8-Dihydroxy-9,10-epoxy-7,8,9,10-tetrahydro-formation (trans-diol epoxide formation) and tetrol (RTTC) formation	1.25±0.27	0.53±0.03	0.42			[151]
CYP1B1 GALN	Yeast cells (<i>S. cerevisiae</i>) expressing human CYP, microsomes	<i>trans</i> -(−)-B[a]P-7,8-diol	<i>trans</i> -(<i>anti</i>)-7,8-Dihydroxy-9,10-epoxy-7,8,9,10-tetrahydro-formation (trans-diol epoxide formation) and tetrol (RTTC) formation	1.29±0.32	0.77±0.06	0.59			[151]
CYP1B1 GALS	Yeast cells (<i>S. cerevisiae</i>) expressing human CYP, microsomes	<i>trans</i> -(−)-B[a]P-7,8-diol	<i>trans</i> -(<i>anti</i>)-7,8-Dihydroxy-9,10-epoxy-7,8,9,10-tetrahydro-formation (trans-Diol epoxide formation) and tetrol (RTTC) formation	1.32±0.32	0.56±0.04	0.42			[151]
CYP1B1*3 (RAVN); Arg48, Ala119, Val432, Ser453	Yeast cells (<i>S. cerevisiae</i>) expressing human CYP, microsomes	<i>trans</i> -(−)-B[a]P-7,8-diol	<i>trans</i> -(<i>anti</i>)-7,8-Dihydroxy-9,10-epoxy-7,8,9,10-tetrahydro-formation (trans-diol epoxide formation) and tetrol (RTTC) formation	2.79±0.80	0.85±0.17	0.33±0.12			[151]
CYP1B1 (RAVS); Arg48, Ala119, Val432, Ser453	Yeast cells (<i>S. cerevisiae</i>) expressing human CYP, microsomes	<i>trans</i> -(−)-B[a]P-7,8-diol	<i>trans</i> -(<i>anti</i>)-7,8-Dihydroxy-9,10-epoxy-7,8,9,10-tetrahydro-formation (trans-diol epoxide formation) and tetrol (RTTC) formation	1.38±0.25	0.88±0.31	0.68±0.35			[151]
CYP1B1 RSVN	Yeast cells (<i>S. cerevisiae</i>) expressing human CYP, microsomes	<i>trans</i> -(−)-B[a]P-7,8-diol	<i>trans</i> -(<i>anti</i>)-7,8-Dihydroxy-9,10-epoxy-7,8,9,10-tetrahydro-formation (trans-diol epoxide formation) and tetrol (RTTC) formation	1.71±0.61	0.72±0.24	0.50±0.36			[151]
CYP1B1*4 (RALS); Arg48, Ala119, Leu432, Ser453	Yeast cells (<i>S. cerevisiae</i>) expressing human CYP, microsomes	<i>trans</i> -(−)-B[a]P-7,8-diol	<i>trans</i> -(<i>anti</i>)-7,8-Dihydroxy-9,10-epoxy-7,8,9,10-tetrahydro-formation (trans-diol epoxide formation) and tetrol (RTTC) formation	1.32±0.41	0.48±0.16	0.40±0.18			[151]
CYP1B1*1 (RALN)Yeast cells (<i>S. cerevisiae</i>) expressing human CYP, microsomes		<i>trans</i> -(−)-B[a]P-7,8-diol	<i>trans</i> -(<i>anti</i>)-7,8-Dihydroxy-9,10-epoxy-7,8,9,10-tetrahydro-formation (trans-diol epoxide formation) and tetrol (RTTC) formation	1.79±0.04	0.76±0.40	0.42±0.22			[151]
CYP1B1*6 (GSVN)Yeast cells (<i>S. cerevisiae</i>) expressing human CYP, microsomes		<i>trans</i> -(−)-B[a]P-7,8-diol	<i>trans</i> -(<i>anti</i>)-7,8-Dihydroxy-9,10-epoxy-7,8,9,10-tetrahydro-formation (trans-diol epoxide formation) and tetrol (RTTC) formation	2.79±0.75	0.63±0.10	0.24±0.06			[151]

Enzyme	Model used	Substrate	Reaction	Inhibitor /Ligand	K_m (μ M); (S_{50} (μ M))	V_{max} (k_{cat} (nmol/min/nmol CYP; l/min, or as specified)	Enzyme efficiency (V_{max}/K_m (ml/min/nmol P450, or as specified)	K_i (μ M); or as specified)	IC_{50} (μ M, or as specified)	Reference
CYP1A1	Baculovirus-infected Sf9 insect cells expressing human CYP and purified, NADPH-P450 reductase purified, dilaurylphosphatidylcholine, 2 μ M substrate	<i>trans</i> -(−)-B[a]P-7,8-diol	<i>trans</i> -(<i>anti</i>)-7,8-Dihydroxy-9,10-epoxy-7,8,9,10-tetrahydro-formation (<i>trans</i> -diol epoxide formation)	St. John's wort, hypericin perforatum extract (Jarsin extract)				3.9±0.2 (μ M); or as specified	3.9±0.2 (μ M); or as specified	24,0±3.0 (μ g/ml)
CYP1A1	Baculovirus-infected Sf9 insect cells expressing human CYP and purified, NADPH-P450 reductase purified, dilaurylphosphatidylcholine, 2 μ M substrate	<i>trans</i> -(−)-B[a]P-7,8-diol	<i>trans</i> -(<i>anti</i>)-7,8-Dihydroxy-9,10-epoxy-7,8,9,10-tetrahydro-formation (<i>trans</i> -diol epoxide formation)	St. John's wort, Hypericin perforatum extract (Aristo extract)				8.0±1.0 (μ M); or as specified	8.0±1.0 (μ M); or as specified	24,0±3.0 (μ g/ml)
CYP1A1	Baculovirus-infected Sf9 insect cells expressing human CYP and purified, NADPH-P450 reductase purified, dilaurylphosphatidylcholine, 2 μ M substrate	<i>trans</i> -(−)-B[a]P-7,8-diol	<i>trans</i> -(<i>anti</i>)-7,8-Dihydroxy-9,10-epoxy-7,8,9,10-tetrahydro-formation (<i>trans</i> -diol epoxide formation)	St. John's wort, hypericin perforatum extract (<i>Esberciu caps</i> , extract)				0.6±0.1 (μ M); or as specified	0.6±0.1 (μ M); or as specified	24,0±3.0 (μ g/ml)
CYP1A1	Baculovirus-infected Sf9 insect cells expressing human CYP and purified, NADPH-P450 reductase purified, dilaurylphosphatidylcholine, 2 μ M substrate	<i>trans</i> -(−)-B[a]P-7,8-diol	<i>trans</i> -(<i>anti</i>)-7,8-Dihydroxy-9,10-epoxy-7,8,9,10-tetrahydro-formation (<i>trans</i> -diol epoxide formation)	Hypericin				3.2±0.8 (μ M); or as specified	3.2±0.8 (μ M); or as specified	24,0±3.0 (μ g/ml)
CYP1A1	Baculovirus-infected Sf9 insect cells expressing human CYP and purified, NADPH-P450 reductase purified, dilaurylphosphatidylcholine, 2 μ M substrate	<i>trans</i> -(−)-B[a]P-7,8-diol	<i>trans</i> -(<i>anti</i>)-7,8-Dihydroxy-9,10-epoxy-7,8,9,10-tetrahydro-formation (<i>trans</i> -diol epoxide formation)	Pseudohypericin				1.1±0.2 (μ M); or as specified	1.1±0.2 (μ M); or as specified	24,0±3.0 (μ g/ml)
CYP1A1	Baculovirus-infected Sf9 insect cells expressing human CYP and purified, NADPH-P450 reductase purified, dilaurylphosphatidylcholine, 2 μ M substrate	<i>trans</i> -(−)-B[a]P-7,8-diol	<i>trans</i> -(<i>anti</i>)-7,8-Dihydroxy-9,10-epoxy-7,8,9,10-tetrahydro-formation (<i>trans</i> -diol epoxide formation)	Quercetin				2.4±0.8 (μ M); or as specified	2.4±0.8 (μ M); or as specified	24,0±3.0 (μ g/ml)

Enzyme	Model used	Substrate	Reaction	K_m (μ M); (S_{50} (μ M))	V_{max} (nmol/min/nmol CYP; l/min, or as specified)	Enzyme efficiency (V_{max}/K_m (ml/min/nmol P450, or as specified)	K_i (μ M); or as specified)	IC_{50} (μ M, or as specified)	Reference
CYP1A1	purified, dilaurylphosphatidylcholine, 2 μ M substrate								
	Baculovirus-infected Sf9 insect cells expressing human CYP and purified, NADPH-P450 reductase purified, dilaurylphosphatidylcholine, 2 μ M substrate	<i>trans</i> -($\rightarrow$)-B[a]P-7,8-diol	<i>trans</i> -(<i>anti</i>)-7,8-Dihydroxy-9,10-epoxy-7,8,9,10-tetrahydro-formation (trans-diol epoxide formation)	1					[61]
CYP1A1	Baculovirus-infected Sf9 insect cells expressing human CYP and purified, NADPH-P450 reductase purified, dilaurylphosphatidylcholine, 5 μ M substrate	B[a]P	3-Hydroxylation	5.2					[61]
CYP1A1	Baculovirus-infected Sf9 insect cells expressing human CYP and purified, NADPH-P450 reductase purified, dilaurylphosphatidylcholine	<i>trans</i> -($\rightarrow$)-B[a]P-7,8-diol	<i>trans</i> -(<i>anti</i>)-7,8-Dihydroxy-9,10-epoxy-7,8,9,10-tetrahydro-formation (trans-Diol epoxide formation)				7,8-Benzoflavone (α -naphthoflavone)	0.8	[61]
CYP1A1	Baculovirus-infected Sf9 insect cells expressing human CYP and purified, NADPH-P450 reductase purified, dilaurylphosphatidylcholine	B[a]P	3-Hydroxylation				Hyperforin	70	[61]
CYP1A1	Baculovirus-infected Sf9 insect cells expressing human CYP and purified, NADPH-P450 reductase purified, dilaurylphosphatidylcholine	B[a]P	3-Hydroxylation				7,8-Benzoflavone (α -naphthoflavone)	1	[61]
CYP1A1.1	Baculovirus-infected Sf9 insect cells expressing human CYP, NADPH-P450 reductase, purified, reconstituted	<i>trans</i> -($\rightarrow$)-B[a]P-7,8-diol	<i>trans</i> -(<i>anti</i>)-7,8-Dihydroxy-9,10-epoxy-7,8,9,10-tetrahydro-formation (trans-diol epoxide formation, high)				Quercetin	2.0 $\pm$ 0.4	[152]
CYP1A1.2	Baculovirus-infected Sf9 insect cells expressing human CYP, NADPH-P450 reductase, purified, reconstituted	<i>trans</i> -($\rightarrow$)-B[a]P-7,8-diol	<i>trans</i> -(<i>anti</i>)-7,8-Dihydroxy-9,10-epoxy-7,8,9,10-tetrahydro-formation (trans-diol epoxide formation)				Quercetin	6.4 $\pm$ 0.6	[152]
CYP1A1.4	Baculovirus-infected Sf9 insect cells expressing human CYP, NADPH-P450 reductase, purified, reconstituted	<i>trans</i> -($\rightarrow$)-B[a]P-7,8-diol	<i>trans</i> -(<i>anti</i>)-7,8-Dihydroxy-9,10-epoxy-7,8,9,10-tetrahydro-formation (trans-diolep oxide formation, high metabolic activation)				Quercetin	9.3 $\pm$ 2.4	[152]
CYP1A1.1	Baculovirus-infected Sf9 insect cells expressing human CYP, NADPH-P450 reductase, purified, reconstituted, 2 μ M substrate	<i>trans</i> -($\rightarrow$)-B[a]P-7,8-diol	<i>trans</i> -(<i>anti</i>)-7,8-Dihydroxy-9,10-epoxy-7,8,9,10-tetrahydro-formation (trans-diol epoxide formation, high metabolic activation)				Quercetin	2.0 $\pm$ 0.4 1.6 $\pm$ 0.3	[152]
CYP1A1.2	Baculovirus-infected Sf9 insect cells expressing human CYP, NADPH-P450 reductase, purified, reconstituted, 2 μ M substrate	<i>trans</i> -($\rightarrow$)-B[a]P-7,8-diol	<i>trans</i> -(<i>anti</i>)-7,8-Dihydroxy-9,10-epoxy-7,8,9,10-tetrahydro-formation (trans-diol epoxide formation, high metabolic activation)				Quercetin	6.4 $\pm$ 0.6 4.4 $\pm$ 0.5	[152]

Enzyme	Model used	Substrate	Reaction	K_m (μ M); (S_{50} (μ M))	V_{max} (k_{cat} (nmol/min/nmol CYP; l/min, or as specific d)	Inhibitor /Ligand	Enzyme efficiency (V_{max}/K_m (ml/min/nmol P450, or as specific d)	K_i (μ M); or as specific d)	IC_{50} (μ M, or as specific d)	Reference
CYP1A1.4	Baculovirus-infected Sf9 insect cells expressing human CYP, NADPH-P450 reductase, purified, reconstituted, 2 μ M substrate	<i>trans</i> (-)-B[a]P-7,8-diol	<i>trans</i> (<i>anti</i>)-7,8-Dihydroxy-9,10-epoxy-7,8,9,10-tetrahydro-formation (trans-diol epoxide formation, high metabolic activation)			Quercetin		9.3 $\pm$ 2.4	7.0 $\pm$ 1.0	[152]
CYP1B1	<i>E. coli</i> (JM109) expressing human CYP, NADPH-P450 reductase, membranes	<i>trans</i> (-)-B[a]P-7,8-diol	Tetrol formation		3.9					[153]
CYP1B1.1	<i>E. coli</i> (JM109) expressing human CYP, NADPH-P450 reductase, membranes	<i>trans</i> (-)-B[a]P-7,8-diol	Tetrol formation		3.0					[153]
CYP1B1.3	<i>E. coli</i> (JM109) expressing human CYP, NADPH-P450 reductase, membranes	<i>trans</i> (-)-B[a]P-7,8-diol	Tetrol formation		3.1					[153]
CYP1B1 432L,453SE	<i>coli</i> (JM109) expressing human CYP, NADPH-P450 reductase, membranes	<i>trans</i> (-)-B[a]P-7,8-diol	Tetrol formation		2.8					[153]
CYP1B1.1	Yeast cells (<i>S. cerevisiae</i>) expressing human CYP, microsomes, +NADPH P450 reductase	B[a]P	<i>trans</i> -7,8-Dihydroxy-7,8-dihydro-(7,8-dihydrodiol) formation		21.1 $\pm$ 3.8		0.086			[84]
CYP1B1.2	Yeast cells (<i>S. cerevisiae</i>) expressing human CYP, microsomes, +NADPH P450 reductase	B[a]P	<i>trans</i> -7,8-Dihydroxy- <i>trans</i> -7,8-Dihydroxy-7,8-dihydro-(7,8-dihydrodiol) formation		23.1 $\pm$ 5.8		0.040			[84]
CYP1B1.3	Yeast cells (<i>S. cerevisiae</i>) expressing human CYP, microsomes, +NADPH P450 reductase	B[a]P	<i>trans</i> -7,8-Dihydroxy- <i>trans</i> -7,8-Dihydroxy-7,8-dihydro-(7,8-dihydrodiol) formation		23.3 $\pm$ 3.13		0.064			[84]
CYP1B1.4	Yeast cells (<i>S. cerevisiae</i>) expressing human CYP, microsomes, +NADPH P450 reductase	B[a]P	<i>trans</i> -7,8-Dihydroxy- <i>trans</i> -7,8-Dihydroxy-7,8-dihydro-(7,8-dihydrodiol) formation		16 $\pm$ 4		0.021			[84]
CYP1B1.6	Yeast cells (<i>S. cerevisiae</i>) expressing human CYP, microsomes, +NADPH P450 reductase	B[a]P	<i>trans</i> -7,8-Dihydroxy- <i>trans</i> -7,8-Dihydroxy-7,8-dihydro-(7,8-dihydrodiol) formation		22 $\pm$ 7		0.055			[84]
CYP1B1.7	Yeast cells (<i>S. cerevisiae</i>) expressing human CYP, microsomes, +NADPH P450 reductase	B[a]P	<i>trans</i> -7,8-Dihydroxy- <i>trans</i> -7,8-Dihydroxy-7,8-dihydro-(7,8-dihydrodiol) formation		47 $\pm$ 7		0.016			[84]
CYP1B1	Yeast cells (<i>S. cerevisiae</i>) expressing human CYP, microsomes	<i>trans</i> (-)-B[a]P-7,8-diol	<i>trans</i> (<i>anti</i>)-7,8-Dihydroxy-9,10-epoxy-7,8,9,10-tetrahydro-formation			7,8-Benzoflavone (α -naphthoflavone)		0.04		[81]
CYP1B1	Yeast cells (<i>S. cerevisiae</i>) expressing human CYP, microsomes	<i>trans</i> (-)-B[a]P-7,8-diol	<i>trans</i> (<i>anti</i>)-7,8-Dihydroxy-9,10-epoxy-7,8,9,10-tetrahydro-formation			Bergamottin, 5-geranoxypsoralen, GF-1-2		587.11		[81]
CYP1B1	Yeast cells (<i>S. cerevisiae</i>) expressing human CYP, microsomes	<i>trans</i> (-)-B[a]P-7,8-diol	<i>trans</i> (<i>anti</i>)-7,8-Dihydroxy-9,10-epoxy-7,8,9,10-tetrahydro-formation			Isopimpinellin		11		[81]
CYP1B1	Yeast cells (<i>S. cerevisiae</i>) expressing human CYP, microsomes	<i>trans</i> (-)-B[a]P-7,8-diol	<i>trans</i> (<i>anti</i>)-7,8-Dihydroxy-9,10-epoxy-7,8,9,10-tetrahydro-formation			Isoimperatorin		6		[81]

Enzyme	Model used	Substrate	Reaction	Inhibitor/Ligand	K_m (μ M); (S_{50} (μ M))	V_{max} (k_{cat} (nmol/min/nmol of CYP; l/min, or as specified)	Enzyme efficiency (V_{max}/K_m (ml/min/nmol P450, or as specified)	K_i (μ M); or as specified)	IC_{50} (μ M, or as specified)	Reference
CYP1B1	Yeast cells (<i>S. cerevisiae</i>) expressing human CYP, microsomes	<i>trans</i> -(+)-B[a]P-7,8-diol	<i>trans</i> -(<i>anti</i>)-7,8-Dihydroxy-9,10-epoxy-7,8,9,10-tetrahydro-formation	Imperatorin				1		[81]
CYP1B1	Yeast cells (<i>S. cerevisiae</i>) expressing human CYP, microsomes	<i>trans</i> -(+)-B[a]P-7,8-diol	<i>trans</i> -(<i>anti</i>)-7,8-Dihydroxy-9,10-epoxy-7,8,9,10-tetrahydro-formation	Isopimpinellin		0.76±0.05		17		[81]
CYP1A1	<i>E. coli</i> (DH5 α F'I'Q) expressing human CYP and NADPH-P450 reductase, bicistronic membranes	<i>trans</i> -(+)-B[a]P-7,8-diol	Metabolic activation	5-Methylchrysene					18±3.5	[89]
CYP1A1	<i>E. coli</i> (DH5 α F'I'Q) expressing human CYP and NADPH-P450 reductase, bicistronic membranes	<i>trans</i> -(+)-B[a]P-7,8-diol	Metabolic activation	Benzol[a]pyrene					18±2.1	[89]
CYP1A1	<i>E. coli</i> (DH5 α F'I'Q) expressing human CYP and NADPH-P450 reductase, bicistronic membranes	<i>trans</i> -(+)-B[a]P-7,8-diol	Metabolic activation	Benz[a]anthracene (1,2-benzanthracene)					18±2.5	[89]
CYP1A1	<i>E. coli</i> (DH5 α F'I'Q) expressing human CYP and NADPH-P450 reductase, bicistronic membranes	<i>trans</i> -(+)-B[a]P-7,8-diol	Metabolic activation	7,8-Benzoflavone (α -naphthoflavone)					4.9±1.5	[89]
CYP1A1	<i>E. coli</i> (DH5 α F'I'Q) expressing human CYP and NADPH-P450 reductase, bicistronic membranes	<i>trans</i> -(+)-B[a]P-7,8-diol	Metabolic activation	3,5,7-Trihydroxyflavone, galangin					1.4±0.31[89]	
CYP1A1	<i>E. coli</i> (DH5 α F'I'Q) expressing human CYP and NADPH-P450 reductase, bicistronic membranes	<i>trans</i> -(+)-B[a]P-7,8-diol	Metabolic activation	5-Methylchrysene					7.9±1.8	[89]
CYP1B1	<i>E. coli</i> (DH5 α F'I'Q) expressing human CYP and NADPH-P450 reductase, bicistronic membranes	<i>trans</i> -(+)-B[a]P-7,8-diol	Metabolic activation	5-Methylchrysene					9.4±2.7	[89]
CYP1B1	<i>E. coli</i> (DH5 α F'I'Q) expressing human CYP and NADPH-P450 reductase, bicistronic membranes	<i>trans</i> -(+)-B[a]P-7,8-diol	Metabolic activation	Benzol[a]pyrene					4.4±0.65[89]	
CYP1B1	<i>E. coli</i> (DH5 α F'I'Q) expressing human CYP and NADPH-P450 reductase, bicistronic membranes	<i>trans</i> -(+)-B[a]P-7,8-diol	Metabolic activation	Benz[a]anthracene (1,2-benzanthracene)					6.4±2.5	[89]
CYP1B1	<i>E. coli</i> (DH5 α F'I'Q) expressing human CYP and NADPH-P450 reductase, bicistronic membranes	<i>trans</i> -(+)-B[a]P-7,8-diol	Metabolic activation	7,8-Benzoflavone (α -naphthoflavone)					1.5±0.22[89]	
CYP1B1	<i>E. coli</i> (DH5 α F'I'Q) expressing human CYP and NADPH-P450 reductase, bicistronic membranes	<i>trans</i> -(+)-B[a]P-7,8-diol	Metabolic activation	3,5,7-Trihydroxyflavone, galangin					0.39±0.1[89]	
CYP1B1	<i>E. coli</i> (DH5 α F'I'Q) expressing human CYP and NADPH-P450 reductase, bicistronic membranes	<i>trans</i> -(+)-B[a]P-7,8-diol	Metabolic activation	5-Methylchrysene					2.7±0.67[89]	
CYP1A1.1	Yeast cells (<i>S. cerevisiae</i>) expressing human CYP, microsomes	B[a]P	C3-Hydroxylation			1.44±0.60	44.6±2.5			[75]
CYP1A1.2	Yeast cells (<i>S. cerevisiae</i>) expressing human CYP, microsomes	B[a]P	C3-Hydroxylation			1.44±0.23	39.5±8.4			[75]

Enzyme	Model used	Substrate	Reaction	Inhibitor/Ligand	K_m (μM); (S_{50} (μM))	V_{max} (k_{cat} (nmol/min/nmol of CYP; l/min, or as specified)	Enzyme efficiency (V_{max}/K_m (ml/min/nmol P450, or as specified)	K_i (μM); (μM , or as specified)	IC_{50} (μM , or as specified)	Reference
CYP1A1	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes, 10 μM substrate	B[a]P	9,10-Dihydrodiol formation			0.47 ± 0.08				[25]
CYP1A1	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes, 10 μM substrate, incubated with microsomal epoxide hydrolase	B[a]P	9,10-Dihydrodiol formation			0.44 ± 0.15				[25]
CYP1A1	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes, 10 μM substrate	B[a]P	7,8-Dihydrodiol formation			0.57 ± 0.10				[25]
CYP1A1	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes, 10 μM substrate, incubated with microsomal epoxid hydrolase	B[a]P	7,8-Dihydrodiol formation			0.38 ± 0.12				[25]
CYP1A1	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes, 10 μM substrate	B[a]P	1,6-Dione (quinone) formation			0.42 ± 0.05				[25]
CYP1A1	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes, 10 μM substrate, incubated with microsomal epoxide hydrolase	B[a]P	1,6-Dione (quinone) formation			0.27 ± 0.08				[25]
CYP1A1	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes, 10 μM substrate	B[a]P	3,6-Dione (quinone) formation			0.73 ± 0.24				[25]
CYP1A1	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes, 10 μM substrate, incubated with microsomal epoxide hydrolase	B[a]P	3,6-Dione (quinone) formation			0.48 ± 0.24				[25]
CYP1A1	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes, 10 μM substrate	B[a]P	6,12-Dione (quinone) formation			0.30 ± 0.07				[25]
CYP1A1	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes, 10 μM substrate, incubated with microsomal epoxide hydrolase	B[a]P	6,12-Dione (quinone) formation			0.22 ± 0.06				[25]
CYP1A1	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes, 10 μM substrate	B[a]P	9-Hydroxylation			0.52 ± 0.08				[25]
CYP1A1	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes, 10 μM substrate, incubated with microsomal epoxide hydrolase	B[a]P	9-Hydroxylation			0.33 ± 0.05				[25]
CYP1A1	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes, 10 μM substrate	B[a]P	3-, 7-Hydroxylation			0.67 ± 0.12				[25]

Enzyme	Model used	Substrate	Reaction	Inhibitor/Ligand	K_m (μM); (S_{50} (μM))	V_{max} (k_{cat} (nmol/min/nmol of CYP; l/min, or as specified)	Enzyme efficiency (V_{max}/K_m (ml/min/nmol P450, or as specified)	K_i (μM); (K_I) (μM , or as specified)	IC_{50} (μM , or as specified)	Reference
CYP1A1	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes, 10 μM substrate, incubated with microsomal epoxide hydrolase	B[a]P	3-, 7-Hydroxylation			0.55 ± 0.02				[25]
CYP1A2	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes, 10 μM substrate	B[a]P	1,6-Dione (quinone) formation			0.10 ± 0.01				[25]
CYP1A2	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes, 10 μM substrate, incubated with microsomal epoxid hydrolase	B[a]P	1,6-Dione (quinone) formation			0.08 ± 0.01				[25]
CYP1A2	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes, 10 μM substrate	B[a]P	3,6-Dione (quinone) formation			0.12 ± 0.01				[25]
CYP1A2	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes, 10 μM substrate, incubated with microsomal epoxide hydrolase	B[a]P	3,6-Dione (quinone) formation			0.12 ± 0.01				[25]
CYP1A2	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes, 10 μM substrate	B[a]P	6,12-Dione (quinone) formation			0.15 ± 0.01				[25]
CYP1A2	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes, 10 μM substrate, incubated with microsomal epoxide hydrolase	B[a]P	6,12-Dione (quinone) formation			0.18 ± 0.04				[25]
CYP1A2	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes, 10 μM substrate	B[a]P	9-Hydroxylation			0.07 ± 0.04				[25]
CYP1A2	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes, 10 μM substrate, incubated with microsomal epoxide hydrolase	B[a]P	9-Hydroxylation			0.10 ± 0.01				[25]
CYP1A2	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes, 10 μM substrate	B[a]P	3-, 7-Hydroxylation			0.12 ± 0.06				[25]
CYP1A2	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes, 10 μM substrate, incubated with microsomal epoxid hydrolase	B[a]P	3-, 7-Hydroxylation			0.14 ± 0.03				[25]
CYP1B1	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes, 10 μM substrate	B[a]P	9,10-Dihydrodiol formation			0.11 ± 0.03				[25]
CYP1B1	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes, 10 μM substrate, incubated with microsomal epoxide hydrolase	B[a]P	9,10-Dihydrodiol formation			0.13 ± 0.04				[25]

Enzyme	Model used	Substrate	Reaction	Inhibitor /Ligand	K_m (μM); (S_{50} (μM))	V_{max} (k_{cat} (nmol/min/nmol of CYP; l/min, or as specified)	Enzyme efficiency (V_{max}/K_m (ml/min/nmol P450, or as specified)	K_i (K_I); (μM , or as specified)	IC_{50} (μM , or as specified)	Reference
CYP1B1	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes, 10 μM substrate	B[a]P	7,8-Dihydrodiol formation			0.18 $\pm$ 0.04				[25]
CYP1B1	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes, 10 μM substrate, incubated with microsomal epoxid hydrolase	B[a]P	7,8-Dihydrodiol formation			0.17 $\pm$ 0.06				[25]
CYP1B1	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes, 10 μM substrate	B[a]P	1,6-Dione (quinone) formation			0.11 $\pm$ 0.01				[25]
CYP1B1	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes, 10 μM substrate, incubated with microsomal epoxid hydrolase	B[a]P	1,6-Dione (quinone) formation			0.11 $\pm$ 0.02				[25]
CYP1B1	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes, 10 μM substrate	B[a]P	3,6-Dione (quinone) formation			0.17 $\pm$ 0.04				[25]
CYP1B1	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes, 10 μM substrate, incubated with microsomal epoxide hydrolase	B[a]P	3,6-Dione (quinone) formation			0.17 $\pm$ 0.04				[25]
CYP1B1	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes, 10 μM substrate	B[a]P	6,12-Dione (quinone) formation			0.18 $\pm$ 0.04				[25]
CYP1B1	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes, 10 μM substrate, incubated with microsomal epoxide hydrolase	B[a]P	6,12-Dione (quinone) formation			0.19 $\pm$ 0.02				[25]
CYP1B1	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes, 10 μM substrate	B[a]P	9-Hydroxylation			0.14 $\pm$ 0.02				[25]
CYP1B1	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes, 10 μM substrate, incubated with microsomal epoxid hydrolase	B[a]P	9-Hydroxylation			0.12 $\pm$ 0.03				[25]
CYP1B1	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes, 10 μM substrate	B[a]P	3-, 7-Hydroxylation			0.18 $\pm$ 0.04				[25]
CYP1B1	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes, 10 μM substrate, incubated with microsomal epoxide hydrolase	B[a]P	3-, 7-Hydroxylation			0.17 $\pm$ 0.03				[25]
CYP1B1	Yeast expressing human CYP, microsomes, 10 μM substrate	B[a]P	9,10-Dihydrodiol formation			0.10 $\pm$ 0.02				[25]

Enzyme	Model used	Substrate	Reaction	K_m (μ M); (S_{50} (μ M))	V_{max} (k_{cat} (nmol/min/nmol of CYP; l/min, or as specified)	Enzyme efficiency (V_{max}/K_m (ml/min/nmol P450, or as specified)	K_i (K_I); (μ M, or as specified)	IC_{50} (μ M, or as specified)	Reference
CYP1B1	Yeast expressing human CYP, microsomes, 10 μ M substrate, incubated with microsomal epoxide hydrolase	B[a]P	9,10-Dihydrodiol formation		0.21 $\pm$ 0.07				[25]
CYP1B1	Yeast expressing human CYP, microsomes, 10 μ M substrate	B[a]P	7,8-Dihydrodiol formation		0.04 $\pm$ 0.02				[25]
CYP1B1	Yeast expressing human CYP, microsomes, 10 μ M substrate, incubated with microsomal epoxide hydrolase	B[a]P	7,8-Dihydrodiol formation		0.31 $\pm$ 0.08				[25]
CYP1B1	Yeast expressing human CYP, microsomes, 10 μ M substrate	B[a]P	1,6-Dione (quinone) formation		0.15 $\pm$ 0.01				[25]
CYP1B1	Yeast expressing human CYP, microsomes, 10 μ M substrate, incubated with microsomal epoxide hydrolase	B[a]P	1,6-Dione (quinone) formation		0.16 $\pm$ 0.01				[25]
CYP1B1	Yeast expressing human CYP, microsomes, 10 μ M substrate	B[a]P	3,6-Dione (quinone) formation		0.13 $\pm$ 0.04				[25]
CYP1B1	Yeast expressing human CYP, microsomes, 10 μ M substrate, incubated with microsomal epoxide hydrolase	B[a]P	3,6-Dione (quinone) formation		0.07 $\pm$ 0.01				[25]
CYP1B1	Yeast expressing human CYP, microsomes, 10 μ M substrate	B[a]P	6,12-Dione (quinone) formation		0.18 $\pm$ 0.02				[25]
CYP1B1	Yeast expressing human CYP, microsomes, 10 μ M substrate, incubated with microsomal epoxide hydrolase	B[a]P	6,12-Dione (quinone) formation		0.16 $\pm$ 0.01				[25]
CYP1B1	yeast expressing human CYP, microsomes, 10 μ M substrate	B[a]P	9-Hydroxylation		0.31 $\pm$ 0.05				[25]
CYP1B1	Yeast expressing human CYP, microsomes, 10 μ M substrate, incubated with microsomal epoxide hydrolase	B[a]P	9-Hydroxylation		0.20 $\pm$ 0.01				[25]
CYP1B1	Yeast expressing human CYP, microsomes, 10 μ M substrate	B[a]P	3-, 7-Hydroxylation		0.45 $\pm$ 0.03				[25]
CYP1B1	Yeast expressing human CYP, microsomes, 10 μ M substrate, incubated with microsomal epoxide hydrolase	B[a]P	3-, 7-Hydroxylation		0.32 $\pm$ 0.07				[25]

Enzyme	Model used	Substrate	Reaction	Inhibitor/Ligand	K_m (μM); (S_{50} (μM))	V_{max} (k_{cat} (nmol/min/nmol of CYP; l/min , or as specified)	Enzyme efficiency (V_{max}/K_m (ml/min/nmol P450, or as specified)	K_i (K_I); (μM , or as specified)	IC_{50} (μM , or as specified)	Reference
CYP1A1	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes, 10 μM substrate	<i>trans</i> -(−)-B[a]P-7,8-diol	Tetrol T-1 formation			1.75 ± 0.29				[25]
CYP1A1	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes, 10 μM substrate	<i>trans</i> -(−)-B[a]P-7,8-diol	Tetrol T-2 formation			0.11 ± 0.01				[25]
CYP1A1	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes, 10 μM substrate	<i>trans</i> -(−)-B[a]P-7,8-diol	Tetrol T-4 formation			0.11 ± 0.01				[25]
CYP1A1	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes, 10 μM substrate	<i>trans</i> -(−)-B[a]P-7,8-diol	Tetrol T-3 formation			0.61 ± 0.10				[25]
CYP1A2	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes, 10 μM substrate	<i>trans</i> -(−)-B[a]P-7,8-diol	Tetrol T-1 formation			0.21 ± 0.02				[25]
CYP1A2	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes, 10 μM substrate	<i>trans</i> -(−)-B[a]P-7,8-diol	Tetrol T-2 formation			0.04 ± 0.02				[25]
CYP1A2	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes, 10 μM substrate	<i>trans</i> -(−)-B[a]P-7,8-diol	Tetrol T-4 formation			0.05 ± 0.02				[25]
CYP1A2	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes, 10 μM substrate	<i>trans</i> -(−)-B[a]P-7,8-diol	Tetrol T-3 formation			0.15 ± 0.01				[25]
CYP1B1	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes, 10 μM substrate	<i>trans</i> -(−)-B[a]P-7,8-diol	Tetrol T-1 formation			0.30 ± 0.02				[25]
CYP1B1	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes, 10 μM substrate	<i>trans</i> -(−)-B[a]P-7,8-diol	Tetrol T-2 formation			0.05 ± 0.02				[25]
CYP1B1	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes, 10 μM substrate	<i>trans</i> -(−)-B[a]P-7,8-diol	Tetrol T-4 formation			0.05 ± 0.02				[25]
CYP1B1	Baculovirus-infected Sf9 insect cells expressing human CYP, microsomes, 10 μM substrate	<i>trans</i> -(−)-B[a]P-7,8-diol	Tetrol T-3 formation			0.18 ± 0.02				[25]
CYP1B1	Yeast expressing human CYP, microsomes, 10 μM substrate	<i>trans</i> -(−)-B[a]P-7,8-diol	Tetrol T-1 formation			0.59 ± 0.04				[25]
CYP1B1	Yeast expressing human CYP, microsomes, 10 μM substrate	<i>trans</i> -(−)-B[a]P-7,8-diol	Tetrol T-2 formation			0.07 ± 0.01				[25]
CYP1B1	Yeast expressing human CYP, microsomes, 10 μM substrate	<i>trans</i> -(−)-B[a]P-7,8-diol	Tetrol T-4 formation			0.10 ± 0.01				[25]
CYP1B1	Yeast expressing human CYP, microsomes, 10 μM substrate	<i>trans</i> -(−)-B[a]P-7,8-diol	Tetrol T-3 formation			0.43 ± 0.03				[25]

Table 4

Number of Entries Related to Metabolism of Xeno- and Endobiotics Available for Searching of the Web Metabolism Database [19]. (Data collected up to 10/01/2017).

Database	Drug metabolizing enzymes		Transporters
	P450s	Other enzymes *	
Substrates	34,644	8,046	14,072
Inhibitors	27,657	5,320	17,959
Activator	539	227	353
Inducers	12,186	2,054	2,103
Total data entries	75,026	15,647	34,487

* Examples of other enzymes which might be searched: AKRs, ADHs, CAs, CDK, CES, COX-2, EPHs, HSDH, NQO1, QR1, PDEs, PFK, SULTs, UGTs, and others.

Number of Entries in Metabolic Databases for Benzo[a]pyrene (B[a]P) and Metabolites. Comparison of Metabolism Data Entries from Offline and Web Metabolism Database [19].

Table 5

Source of data	Number of data entries				
	P450	EH	AKRs	UGT	SULT
Human data; Excel formatted database, collected up to 2008	213	-	10	-	-
Human data; Web searchable database, collected up to 10/01/2017)	345	3	10	3	3
Other species data; Web searchable database collected up to 10/01/2017	287	7	-	14	10

* Data refers to all interactions of the compound as substrate, inhibitor and/or inducer.

Table 6

Number of Entries of Benzo[*a*]pyrene (B[*a*]P) and/or Metabolites Interacting with Human Metabolism Enzymes as Substrates, Inhibitors, Inducers, and Yielding Activations [19]. (Data Collected up to 10/01/2017).

Enzyme	As substrate	As inhibitor	As inducer	Activation *
CYP1A1	97	16 (of which potent 10 as inhibition)	59 (AhR agonist, potent inducer of activity, mRNA expression, protein expression)	7 (potent or weak activation)
CYP1A2	21	7 (potent mechanism based inhibition)	10 (AhR agonist, inducer of mRNA, protein expression)	4 (potent or weak activation)
CYP1B1	82	8 (potent inhibition)	28 (inducer of activity, mRNA expression, protein expression)	8 (potent or weak activation)
CYP2B6	5	-	-	-
CYP2C8	16	-	-	6 (weak activation)
CYP2D6	1	-	-	1 (weak activation)
CYP2E1	3	-	-	-
CYP2F3	1	-	-	-
CYP2S1	3	-	-	-
CYP2W1	3	-	-	2 (weak activation)
CYP3A4	11	1 (medium inhibitor)	-	-
CYP3A5	2	-	-	1 (weak activation)
CYP3A7	2	-	-	-
CYP11B2	-	-	1	-
CYP19A1 (aromatase)	-	1	1 (weak inducer)	-
AKRs	7	-	-	-
EH	3	-	-	-
UGTs	3	-	-	-
SULTs	2	-	-	-

* Activation to potentially toxic metabolites or intermediates.