Review

Formation of Potentially Toxic Metabolites of Polycyclic Aromatic Compounds (PAHs) in Reactions Catalyzed by Human Metabolizing Enzymes

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Review

Formation of Potentially Toxic Metabolites of Polycyclic Aromatic Compounds (PAHs) in Reactions Catalyzed by Human Metabolizing Enzymes

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Abstract: Data are presented on the formation of potentially toxic metabolites of polycyclic aromatic hydrocarbons (PAHs) and the effects of the structure of the compounds on the human metabolic enzymes that catalyze the reactions and the products formed. The tabular data lists the formation of potentially toxic/reactive products. The data obtained from in vitro experiments showed that the oxidative reactions predominate (67% of the potentially toxic reactions). Sulfating reactions participate in 14%, reductions with 12%, and acetylation reactions with 7%. Of the enzymes, cytochrome P450 (P450, CYP) enzymes catalyzed 58% of the reactions, aldo-keto reductases (AKR) 16%, sulfotransferases (SULT) 15%, *N*-acetyltransferases (NAT) 6%, cytochrome P450 reductase (NPR) 3%, and a group of minor participating enzymes to the extent of 3%. Within the P450 Superfamily, P450 Family 1 (P450 1A1, 1A2, 1B1) participates to the extent of 75%, P450 3A4 with 8%, P450 2W1 with 4%, and the group of minor participating enzymes with 13%. In the C- and *N*-atom(s)-containing PAHs (*N*-PAHs), the P450 enzymes dominated with 66%, followed by NAT (14%), SULT (11%), and the group of minor participating enzymes (9%). The P450 Family 1 dominated with 67%. In the *C*- atom-containing group of PAHs (*C*-PAHs), the P450 enzymes participated with 51%. AKR with 28%, SULT with 19%, and COX and EH enzymes with 2%. Of the P450 Family 1 enzymes, P450 1A1 dominated with 41% of the reactions. The data show the dominant participation of the P450 enzymes and the effect of the N-atom presence on the toxication reactions of PAHs and the metabolites formed. Selected examples of the PAHs that are activated or proposed to form toxic species are discussed.

Keywords: polycyclic aromatic hydrocarbons; PAHs; toxic metabolites; human enzymes

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The polycyclic aromatic hydrocarbons (PAHs) in the human surrounding nature are produced by different human activities, e.g. incomplete combustion processes of organic materials such as coal, oil, gas, wood, garbage, food (e.g., grilled meat and charred food), and tobacco smoke. Approaches to studying the connection between the metabolism of different types of chemicals including PAHs, and the role of individual human metabolism enzymes in the processes have been extensively studied [1–8]. The data obtained allowed the presumption that chemical carcinogens are activated to toxic species in reactions catalyzed by multiple enzymes. These identified as the major ones are P450, SULT, AKR, and NAT enzymes. In addition, a relationship between structural characteristics and the chemical nature of the toxicant and toxication reaction was identified. For instance, epoxidation reactions involve olefins and aryl rings, nitro reductions involve nitro groups, *N*-hydroxylation reactions involve aryl amines and heterocyclic amines, *O*-sulfation involves hydroxyl arylamines and benzylic alcohols, while *Cα*-hydroxylation is prominent for *N*-nitrosamines. Analysis of the type of toxication reactions of chemical carcinogens revealed the following reactions: *C*-hydroxylation, *N*-hydroxylation, *O*-acetylation, *O*-sulfation, nitroreduction, and other reductions. Most of the reactions are oxidations, accounting for 73%, of which the most prominent were *C*-hydroxylation and *N*-hydroxylation. It was shown that chemical carcinogens, as a group of compounds, are dominantly activated by cytochrome P450 enzymes of which P450 1A1, 1A2, 1B1, 2A6, 2E1, and 3A4 accounted

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for 77% of the reactions [4]. Benzo[*a*]pyrene (B[*a*]P), as a representative toxic environmental carcinogen, has been extensively investigated and discussed over time (Table 2 and references therein). In summary, the data related to the metabolism and toxicity data of B[*a*]P revealed the major role of Family 1 P450s (P450 1A1, 1A2, 1B1) in the metabolism of the compound with minor participation of P450 2C8, 2C9, 2C19, 2D6, 2E1, and 3A4 [6].

The present report updates and analyses the published data on metabolic toxication of PAHs as a group of environmental pollutants with suspected/proven toxic properties (mutagenic, genotoxic, carcinogenic) by human metabolizing enzymes along with the well-studied P450 enzymes. The data on 60 human enzymes that catalyze oxidative, reductive, hydrolysis, and conjugation reactions of PAHs resulting in the formation of potentially toxic metabolites or intermediates are included in the analysis (Table 1).

Table 1. Abbreviations used in the text and tables.

Enzyme	Enzyme Name
AADAC	Arylacetamide deacetylase
ADH	Alcohol dehydrogenase
AKR	Aldo-keto reductase
AKR1A1	Aldo-keto reductase 1A1
AKR1B1	Aldo-keto reductase 1B1
AKR1B10	Aldo-keto reductase 1B10
AKR1C1	Aldo-keto reductase 1C1
AKR1C2	Aldo-keto reductase 1C2
AKR1C3	Aldo-keto reductase 1C3
AKR1C4	Aldo-keto reductase 1C4
AOX1	Aldehyde oxidase 1
CES1A	Carboxylesterase 1A
CES2	Carboxylesterase 2
COX	Cyclooxygenase
COX-1	Cyclooxygenase 1
COX-2	Cyclooxygenase 2
EH	Epoxide hydrolase
FMO1	Flavin-containing monooxygenase 1
FMO2	Flavin-containing monooxygenase 2
FMO3	Flavin-containing monooxygenase 3
Hb	Hemoglobin
LPO	Lactoperoxidase
MAO A	Monoamine oxidase A
MPO	Myeloperoxidase
NAT	*N*-acetyltransferase
NAT1	*N*-acetyltransferase 1
NAT2	*N*-acetyltransferase 2
NAR	Nitrate reductase
NQO	NAD(P)H quinone oxidoreductase

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NQO1	NAD(P)H quinone oxidoreductase 1
NPR, POR	NAD(P)H-P450 reductase
NR	Nitrate reductase
P450	Cytochrome P450
P450 1A1	Cytochrome P450 1A1
P450 1A2	Cytochrome P450 1A2
P450 1B1	Cytochrome P450 1B1
P450 2A6	Cytochrome P450 2A6
P450 2B6	Cytochrome P450 2B6
P450 2C10	Cytochrome P450 2C10
P450 2C18	Cytochrome P450 2C18
P450 2C19	Cytochrome P450 2C19
P450 2C8	Cytochrome P450 2C8
P450 2C9	Cytochrome P450 2C9
P450 2C9.1	Cytochrome P450 2C9.1
P450 2C9.2	Cytochrome P450 2C9.2
P450 2C9.3	Cytochrome P450 2C9.3
P450 2D6	Cytochrome P450 2D6
P450 2E1	Cytochrome P450 2E1
P450 2F1	Cytochrome P450 2F1
P450 2J2	Cytochrome P450 2J2
P450 3A4	Cytochrome P450 3A4
P450 3A5	Cytochrome P450 3A5
P450 3A7	Cytochrome P450 3A7
P450 4A11	Cytochrome P450 4A11
P450 4B1	Cytochrome P450 4B1
P450 2W1	Cytochrome P450 2W1
PGHS	Prostaglandin H synthase
PO	Peroxidase
SULT	Sulfotransferases
SULT1A1	Sulfotransferase 1A1
SULT1A2	Sulfotransferase 1A2
SULT1A3	Sulfotransferase 1A3
SULT1B1	Sulfotransferase 1B1
SULT1C1	Sulfotransferase 1C1
SULT1C2	Sulfotransferase 1C2
SULT1C3	Sulfotransferase 1C3
SULT1E1	Sulfotransferase 1E1
SULT2A1	Sulfotransferase 2A1
SULT2E1	Sulfotransferase 2E1

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XOR	Xanthine oxidoreductase

The analysis results are summarized in 290 alphabetically organized and tabularly presented records (Table 2).

Table 2. Examples of participation of human drug-metabolizing enzymes in forming potentially toxic products of polycyclic aromatic hydrocarbons (PAHs) and metabolites.

Compound or Metabolite	**Compound Category/Source /Metabolite/Toxic Effects**	**Enzyme**	**Reactions and Reactive /Toxic Product(s) Formation**	**References**
(-)-1-Hydroxyethylpyrene	Metabolite of ethylpyrene, research chemical	SULT1A1	*O*-Sulfation, sulfo-conjugate, electrophilic nitrenium ion formation	[14,15]
(-)-1-Hydroxyethylpyrene	As above	SULT1A2	*O*-Sulfation, sulfo-conjugate, electrophilic nitrenium ion formation	[15]
(-)-1-Hydroxyethylpyrene	As above	SULT1C1	*O*-Sulfation, sulfo-conjugate, electrophilic nitrenium ion formation	[15]
(-)-1-Hydroxyethylpyrene	As above	SULT1C2	*O*-Sulfation, sulfo-conjugate, electrophilic nitrenium ion formation	[15]
(-)-*R,R* and (+)-*S,S*-Benzo[*g*]chrysene-11,12-diol	Metabolite of B[*g*]C, fossil fuels, and organic materials combustion product	AKR1B1	Oxidation, *o*-quinone	[16]
(−)-*R,R*- and (+)-*S,S*-Benzo[*g*]chrysene-11,12-diol	As above	AKR1B10	Oxidation, *o*-quinone	[16]

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(+)-Benz[*a*]anthracene-3*S*,4*S*-diol	Metabolite of B[*a*]A, fossil fuels, and organic materials combustion products tobacco, smoke constituent	AKR1B1	Oxidation, *o*-quinone	[16]
(+)-Benz[*a*]anthracene-3S,4*S*-diol	As above	AKR1B10	Oxidation, *o*-quinone	[16]
(+)-Benzo[*a*]pyrene-7*S*,8*S*-dihydrodiol	Metabolite of B[*a*]P	AKR1B1	Oxidation, *o*-quinone	[16]
(+)-Benzo[*a*]pyrene-7*S*,8*S*-dihydrodiol	As above	AKR1B10	Oxidation, *o*-quinone	[16]
(±)- and (-)-Benzo[*a*]pyrene-7,8-dihydrodiol ((±)- and (-)-B[*a*]P-7,8-diol)	As above	AKR1C1	Oxidation, *o*-quinone, and reactive oxygen species (ROS)	[16–20]
(±)- and (-)-Benzo[*a*]pyrene-7,8-dihydrodiol ((±)- and (-)-B[*a*]P-7,8-diol)	As above	AKR1C3	Oxidation, *o*-quinone, and reactive oxygen species (ROS)	[16,17,19,20]
(±)- and (-)-Benzo[*a*]pyrene-7,8-dihydrodiol ((±)- and (-)-B[*a*]P-7,8-diol)	As above	AKR1C4	Oxidation, *o*-quinone, and reactive oxygen species (ROS)	[16,17,19,20]
(±)- and (-)-Benzo[*a*]pyrene-7,8-dihydrodiol ((±)- and (-)-B[*a*]P-7,8-diol)	As above	AKR1C2	Oxidation, *o*-quinone, and reactive oxygen species (ROS)	[16,17,19,20]
(±)- and (-)-Benzo[*a*]pyrene-7,8-dihydrodiol ((±)- and (-)-B[*a*]P-7,8-diol)	As above	MAO 2	Oxidation, peroxyl radicals	[21]
(±)- and (-)-Benzo[*a*]pyrene-7,8-dihydrodiol ((±)- and (-)-B[*a*]P-7,8-diol)	As above	COX-1	Oxidation, peroxyl radicals	[21]

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(±)-, (-)-, and (+)-Benzo[*a*]pyrene-7,8-dihydrodiol ((±)-, (-)-, and (+)-B[a]P-7,8-diol)	As above	P450 1A1	*trans*-(*anti*)-7,8-Dihydroxy-9,10-epoxy-7,8,9,10-tetrahydro-formation, *trans*-diolepoxide, oxidation *	[1,3,22–25,27–32,34,35,38,39,127]
(±)-, (-)-, and (+)-Benzo[*a*]pyrene-7,8-dihydrodiol ((±)-, (-)-, and (+)-B[a]P-7,8-diol)	As above	P450 1A2	*trans*-(*anti*)-7,8-Dihydroxy-9,10-epoxy-7,8,9,10-tetrahydro-formation, *trans*-diol epoxide, oxidation	[1,22–24,38,40–42]
(±)-, (-)-, and (+)-Benzo[*a*]pyrene-7,8-dihydrodiol ((±)-, (-)-, and (+)-B[*a*]P-7,8-diol)	As above	P450 1B1	*trans*-(*anti*)-7,8-Dihydroxy-9,10-epoxy-7,8,9,10-tetrahydro-formation, *trans*-diol epoxide (low Km, high activity, high efficiency), oxidation *	[1,24,25,27,31,36–38,41,43–45]
(±)-, (+)- and (-)-1-Hydroxyethylpyrene	Metabolite of ethylpyrene, research chemicals	SULT2A1	*O*-Sulfation, sulfo-conjugate, electrophilic nitrenium ion formation	[14,15,46]
(±)-, (+)- and (-)-1-Hydroxyethylpyrene	As above	SULT1C3	*O*-Sulfation, sulfo-conjugate, electrophilic nitrenium ion formation	[46]
(±)-, (+)- and (-)-1-Hydroxyethylpyrene	As above	SULT1E1	*O*-Sulfation, sulfo-conjugate, electrophilic nitrenium ion formation *	[14,15,46]

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(±)-Benzo[*a*]pyrene-7,8-dihydrodiol ((±)-B[*a*]P-7,8-diol)	Metabolite of B[*a*]P	AKR1A1	Oxidation, *o*-quinone formation, preferential for (-)-7*R*,8*R*-oxidation *	[16,17,31,36,37,47,48]
(±)-Benzo[*a*]pyrene-7,8-dihydrodiol ((±)-B[*a*]P-7,8-diol)	As above	AKR1C4	Oxidation, *o*-quinone formation	[16]
(±)-Benzo[*a*]pyrene-7,8-dihydrodiol ((±)-B[*a*]P-7,8-diol)	As above	P450 2W1	Oxidation, diolepoxide formation	[43]
1,10-Diazachrysene [1,10-DAC)	Chrysene derivative	P450 1A2	Oxidation, enamine epoxide formation	[11,12]
1,2-Dihydro-1,2-dihydroxy-6-nitrochrysene (trans)	Metabolite of 6-nitrochrysene, nitroarene	P450 3A4	Oxidation	[50]
1,6-Dinitropyrene (1,6-DNP)	Environmental pollutants, diesel engine combustion by-products, nitroarene, pyrene derivative	P450 3A4	Nitroreduction, aminopyrene, 4-hydroxylamine, formation	[13]
1,6-Dinitropyrene (1,6-DNP)	As above	P450 1B1 (co-expressed with NPR)	1-Aminopyrene formation, nitroreduction/*O*-acetylation, at low concentrations, electrophilic nitrenium ion formation	[9]
1,6-Dinitropyrene (1,6-DNP)	As above	NPR	Reduction to 1-Nitro-6-nitrosopyrene, reactive oxygen species formation	[51]
1,8-Dinitropyrene (1,8-DNP)	As above	NPR	Reduction to 1-Nitro-8-nitrosopyrene, reactive oxygen species formation	[51]

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1,8-Dinitropyrene (1,8-DNP)	As above	NPR	1-Aminopyrene formation, nitroreduction/*O*-acetylation, at low concentrations, electrophilic nitrenium ion formation *	[9]
1,8-Dinitropyrene (1,8-DNP)	As above	P450 3A4	Epoxidation C4,5-, oxidation, minor reaction	[10,13,52]
1,8-Dinitropyrene (1,8-DNP)	As above	NAT1	*O*-Acetylation after nitroreduction, electrophilic nitrenium ion formation	[53]
1,8-Dinitropyrene (1,8-DNP)	As above	NAT2	O-Acetylation after nitroreduction, electrophilic nitrenium ion formation *	[53]
1,8-Dinitropyrene (1,8-DNP)	As above	P450 1A1 (co-expressed with NPR)	1-Aminopyrene formation, nitroreduction/*O*-acetylation, at low concentrations, electrophilic nitrenium ion formation *	[9]
10-Azabenzo[*a*]pyrene	Environmental pollutants, gasoline exhaust, and cooking emissions compounds, aza-aromatic	P450 1A2	Oxidation at pyridine moiety **	[54]
10-Azabenzo[*a*]pyrene	As above	P450 1A1	Oxidation, minor enzyme *	[54]

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10-Hydroxy-7,8,9,10-tetrahydrobenzo[*a*]pyrene	Metabolite of B[a]P	SULT1E1	*O*-Sulfation, sulfo-conjugate, electrophilic nitrenium ion formation	[55]
12-Methylbenz[*a*]anthracene-3,4-diol	Metabolite of 12-methylbenz[*a*]anthracene	AKR1A1	Oxidation, *o*-quinone formation	[48]
1-Acetylpyrene	Industrial chemicals, carbonyl-pyrene	SULT2E1 (in the presence of NADPH-fortified human liver cytosol)	*O*-Sulfation, sulfo-conjugate, electrophilic nitrenium ion formation * (after reduction)	[56]
1-Aminopyrene	Metabolite of 1-nitropyrene, industrial chemicals, arylamine	P450 1A1	Oxidation, *N*-hydroxylation, and nitrenium ion formation via *O*-acetylation, electrophilic nitrenium ion formation	[10]
1-Aminopyrene	As above	P450 1A2	Oxidation, *N*-hydroxylation, and nitrenium ion formation via *O*-acetylation, electrophilic nitrenium ion formation *	[10,57–59]
1-Aminopyrene	As above	P450 1B1	Oxidation, *N*-hydroxylation, and nitrenium ion formation via *O*-acetylation, electrophilic nitrenium ion formation *	[10]
1-Aminopyrene	As above	P450 3A4	Oxidation, N-hydroxylation	[10]

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1-Formylpyrene	Fluorescent dye, carbonyl-pyrene	SULT2A1	*O*-Sulfation, sulfo-conjugate, electrophilic nitrenium ion formation (after reduction)	[56]
1-Hydroxy-3-methylcholanthrene (1-OH-MC)	Metabolite of 3-MC	SULT2A1	*O*-Sulfation, sulfo-conjugate, electrophilic nitrenium ion formation, electrophilic nitrenium ion formation	[56]
1-Hydroxymethylpyrene (1-HMP)	Metabolite of 1-MP	SULT1A1	O-Sulfation, sulfo-conjugate, electrophilic nitrenium ion formation *	[14,15,46,60,63]
1-Hydroxymethylpyrene (1-HMP)	As above	SULT1A2	*O*-Sulfation, sulfo-conjugate, electrophilic nitrenium ion formation	[15,56,63]
1-Hydroxymethylpyrene (1-HMP)	As above	SULT1A3	*O*-Sulfation, sulfo-conjugate, electrophilic nitrenium ion formation	[14,15,60]
1-Hydroxymethylpyrene (1-HMP)	As above	SULT2E1	*O*-Sulfation, sulfo-conjugate, electrophilic nitrenium ion formation *	[56]
1-Hydroxymethylpyrene (1-HMP)	As above	SULT1C2	O-Sulfation, sulfo-conjugate, electrophilic nitrenium ion formation	[56]

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1-Hydroxymethylpyrene (1-HMP)	As above	SULT2A1	*O*-Sulfation, sulfo-conjugate, electrophilic nitrenium ion formation, electrophilic nitrenium ion formation *	[56]
1-Methylpyrene (1-MP)	Wood, diesel oil, and gasoline fuels incomplete combustion products, pyrene derivatives.	SULT2A1	*O*-Sulfation, sulfo-conjugate, electrophilic nitrenium ion formation * (after hydroxylation)	[14,15,60]
1-Nitro-6-nitrosopyrene	Metabolite of 1,6-dinitropyrene, nitroarene, pyrene derivative	POR	Nitroreduction, reactive oxygen species formation	[51]
1-Nitro-8-nitrosopyrene	Metabolite of 1,8-dinitropyrene, nitroarene	POR	Nitroreduction, reactive oxygen species formation	[51]
1-Nitropyrene (1-NP)	Environmental pollutants, diesel engine combustion by-products, nitroarene, pyrene derivative	P450 1B1 (co-expressed with NPR)	1-Aminopyrene formation, nitroreduction, and *O*-acetylation, at low concentrations, electrophilic nitrenium ion formation, epoxidation at high concentrations*	[10]
1-Nitropyrene (1-NP)	As above	P450 1A1	Oxidation, ring oxidation *	[10,13,64]
1-Nitropyrene (1-NP)	As above	P450 1B1 (co-expressed with NPR)	Oxidation, nitroreduction,	[10,64]

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			epoxidation, ring oxidation *,**	
1-Nitropyrene (1-NP)	As above	P450 3A4	Oxidation, epoxidation, ring oxidation *	[10]
2,3-Dihydroxy-2,3-dihydrofluoranthene	Metabolite of fluoranthene	P450 1B1	Oxidation	[3]
2-Acetylaminofluorene (2-AAF)	Metabolite of aminofluorene, arylamine	P450 1A2	*N*-Hydroxylation, oxidation *	[24,40,52,65,67–69]
2-Acetylaminofluorene (2-AAF)	As above	NAT1	*O*-Acetylation after *N*-hydroxylation, electrophilic nitrenium ion formation, electrophilic nitrenium ion formation *	[69]
2-Acetylaminofluorene (2-AAF)	As above	P450 1A1	*N*-Hydroxylation, oxidation	[1,24,67]
2-Aminoanthracene (2AA)	Research chemicals, arylamine	P450 1A1	*N*-Hydroxylation, oxidation *	[1,3,24,70]
2-Aminoanthracene (2AA)	As above	P450 1A2	*N*-Hydroxylation, oxidation (high activity) *,**	[10,24,40,57–59,65,70–72]
2-Aminoanthracene (2AA)	As above	P450 1B1	*N*-Hydroxylation, oxidation (high activity) *	[1,24,43,70]
2-Aminoanthracene (2AA)	As above	P450 2E1	*N*-Hydroxylation, oxidation	[70]
2-Aminoanthracene (2AA)	As above	P450 2W1	Oxidation	[43]
2-Aminodipyrido[1,2-*a*:3,2'-d]-imidazole (Glu-P-2)	Cooked meat and fish compounds, a component of	P450 1A2	Oxidation	[40,52,65]

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	tobacco smoke, heterocyclic amine			
2-Aminofluorene (2-AF)	Research chemicals, fluorene derivative, arylamine	P450 1A1	*N*-Hydroxylation, oxidation	[1,24,25,70]
2-Aminofluorene (2-AF)	As above	P450 1B1	*N*-Hydroxylation, oxidation *	[1,24,25,43,70]
2-Aminofluorene (2-AF)	As above	P450 2E1	*N*-Hydroxylation, oxidation *	[70]
2-Aminofluorene (2-AF)	As above	P450 2W1	Oxidation, diolepoxide formation	[43]
2-Aminofluorene (2-AF)	As above	P450 3A4	Oxidation, ring oxidation	[70,73]
2-Aminofluorene (2-AF)	As above	P450 3A7	Oxidation, ring oxidation	[73]
2-Aminofluorene (2-AF)	As above	P450 4B1	*N*-Hydroxylation, oxidation	[74,75]
2-Aminofluorene (2-AF)	As above	NAT1	*O*-Acetylation after *N*-hydroxylation, electrophilic nitrenium ion formation	[76,77]
2-Hydroxy-3-methylcholanthrene 2-OH-MC)	Metabolite of 3-MC	SULT2A1	*O*-Sulfation, sulfo-conjugate, electrophilic nitrenium ion formation	[56]
2-Hydroxymethylpyrene, 2-pyrenemethanol	Metabolite of methylpyrene, research chemical	SULT2A1	*O*-Sulfation, sulfo-conjugate, electrophilic nitrenium ion formation	[55]
2-Naphthylamine (*β*-NA)	Industrial chemicals, used in the production of azo dyes,	P450 1A2	*N*-Hydroxylation, oxidation	[40,52,65,69,70,82]

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	tobacco smoke compounds, arylamine			
2-Naphthylamine (*β*-NA)	As above	NAT1	*O*-Acetylation after *N*-Hydroxylation, electrophilic nitrenium ion formation	[69]
2-Nitroanisole	Environmental pollutants, industrial chemicals, nitroarene	XOR	Nitroreduction to hydroxylamine	[83]
2-Nitrobenzanthrone (2-NBA)	Ambient air pollutants, nitroarene	NAT2	*O*-Acetylation (after nitroreduction to hydroxylamine), electrophilic nitrenium ion formation	[84]
2-Nitrobenzanthrone (2-NBA)	As above	SULT1A1	*O*-Sulfation, sulfo-conjugate (after nitroreduction to hydroxylamine), electrophilic nitrenium ion formation	[84]
2-Nitrofluoranthene (2-NF)	As above	P450 1B1 (co-expressed with NPR)	1-Aminopyrene formation, nitroreduction/*O*-acetylation, at low concentrations	[9]
2-Nitrofluorene (2-NF)	As above	NAT1	*O*-Acetylation after nitroreduction, electrophilic nitrenium ion formation	[77]
2-Nitronaphthalene	Industrial chemicals, nitroarene	P450 1A1	Oxidation	[78]
2-Nitropyrene (2-NP)	Environmental pollutants,	P450 1A1	Oxidation, ring oxidations	[24,64]

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	diesel engine combustion by-products, nitroarene			
2-Nitropyrene (2-NP)	As above	P450 1B1	Oxidation, ring oxidations *	[1,24,64]
3,6-Dinitrobenzo[*e*]pyrene (DNB*e*P)	Environmental pollutants, surface soil, and airborne particle contaminants, nitroarene	P450 1A1, NPR, OAT2	Nitroreduction and *O*-acetylation by NAT enzymes, electrophilic nitrenium ion formation	[79]
3,6-Dinitrobenzo[*e*]pyrene (DNB*e*P)	As above	P450 1A2, NPR, OAT2	Nitroreduction and *O*-acetylation by NAT enzymes, electrophilic nitrenium ion formation	[79]
3,6-Dinitrobenzo[*e*]pyrene (DNB*e*P)	As above	P450 3A4, NPR, OAT2	Nitroreduction and *O*-acetylation by NAT enzymes, electrophilic nitrenium ion formation	[79]
3,6-Dinitrobenzo[*e*]pyrene (DNB*e*P)	As above	POR	Nitroreduction and *O*-acetylation by NAT enzymes, electrophilic nitrenium ion formation	[79,80]
3,9-Dinitrofluoranthene	Environmental pollutants, combustion fossil fuels (e.g., diesel engine) products, and research chemicals, fluoranthene	SULT1A1	O-Sulfation, sulfo-conjugate, electrophilic nitrenium ion formation, electrophilic nitrenium ion formation * (after nitroreduction to hydroxylamine)	[81]

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	derivative, nitroarene			
3-Acetylaminobenzanthrone (3-Ac-ABA)	Metabolite of 3-nitrobenzanthrone (3-NBA), arylamine	P450 1A2	*N*-Hydroxylation after deacetylation concentration-dependent), oxidation	[85,87]
3-Acetylaminobenzanthrone (3-Ac-ABA)	As above	NAT1	*O*-Acetylation after deacetylation and *N*-hydroxylation, at higher concentrations, electrophilic nitrenium ion formation *	[85]
3-Acetylaminobenzanthrone (3-Ac-ABA)	As above	NAT2	*O*-Acetylation after deacetylation and *N*-hydroxylation, at higher concentrations, electrophilic nitrenium ion formation *	[85]
3-Acetylaminobenzanthrone (3-Ac-ABA)	As above	SULT1A1	O-Sulfation, sulfo-conjugate, after deacetylation and N-hydroxylation, at higher concentrations, electrophilic nitrenium ion formation *	[85]
3-Acetylaminobenzanthrone (3-Ac-ABA)	As above	SULT1A2	*O*-Sulfation, sulfo-conjugate, after deacetylation and *N*-hydroxylation, at higher concentrations *	[56,88]
3-Aminobenzanthrone (3-ABA)	Metabolite of 3-nitrobenzanthr	P450 1A1	*N*-Hydroxylation, oxidation **	[87–89]

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	one (3-NBA) found in diesel fuel exhaust, benzanthrone derivative, arylamine			
3-Aminobenzanthrone (3-ABA)	As above	P450 1A2	*N*-Hydroxylation, oxidation, concentration-dependent **	[87,88]
3-Aminobenzanthrone (3-ABA)	As above	P450 1B1	*N*-Hydroxylation, oxidation	[89]
3-Aminobenzanthrone (3-ABA)	As above	P450 2A6	*N*-Hydroxylation, oxidation	[89]
3-Aminobenzanthrone (3-ABA)	As above	P450 2B6	*N*-Hydroxylation, oxidation	[89]
3-Aminobenzanthrone (3-ABA)	As above	LPO	*N*-Oxidation	[87,88]
3-Aminobenzanthrone (3-ABA)	As above	MPO	*N*-Oxidation	[87,88]
3-Aminobenzanthrone (3-ABA)	As above	NAT1	*O*-Acetylation after *N*-hydroxylation, at higher concentrations, electrophilic nitrenium ion formation *	[85]
3-Aminobenzanthrone (3-ABA)	As above	NAT2	*O*-Acetylation after *N*-hydroxylation, at higher concentrations, electrophilic nitrenium ion formation	[85]

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3-Aminobenzanthrone (3-ABA)	As above	PGHS	*N*-Oxidation	[87,88]
3-Aminobenzanthrone (3-ABA)	As above	SULT1A1	*O*-Sulfation, sulfo-conjugate, after *N*-hydroxylation, at higher concentrations *	[85]
3-Aminobenzanthrone (3-ABA)	As above	SULT1A2	O-Sulfation, sulfo-conjugate, after *N*-hydroxylation, at higher concentrations, electrophilic nitrenium ion formation *	[85]
3-Methylcholanthrene (3-MC)	Environmental pollutants, incomplete burning organic compounds products coal tar, heavy-end petroleum compounds, cigarette smoke compounds, and research chemical	P450 1A1	Oxidation, micronucleus frequency increased in CHL-A1 cells	[90]
3-Methylcholanthrene-11,12-diol (3-MC-11,12-diol)	Metabolite of 3-MC	P450 1A1	Oxidation	[1]
3-Nitrobenzanthrone (3-NBA)	Environmental pollutants, found in diesel fuel exhaust, urban air	P450 1A1	Nitroreduction to hydroxylamine	[86,87]

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	pollutants, nitroarene			
3-Nitrobenzanthrone (3-NBA)	As above	P450 1A2	Nitroreduction to hydroxylamine	[85–87]
3-Nitrobenzanthrone (3-NBA)	As above	P450 2B6	Nitroreduction to hydroxylamine *	[86]
3-Nitrobenzanthrone (3-NBA)	As above	P450 2D6	Nitroreduction to hydroxylamine *	[86]
3-Nitrobenzanthrone (3-NBA)	As above	POR	Nitroreduction to hydroxylamine	[86]
3-Nitrobenzanthrone (3-NBA)	As above	XOR	Nitroreduction to hydroxylamine	[85]
3-Nitrobenzanthrone (3-NBA)	As above	NAT1	*O*-Acetylation after nitro-reduction to hydroxylamine, at higher concentrations, electrophilic nitrenium ion formation *	[85,87,91]
3-Nitrobenzanthrone (3-NBA)	As above	NAT2	*O*-Acetylation after nitro-reduction to hydroxylamine, at higher concentrations, electrophilic nitrenium ion formation *	[84,85,87,91]
3-Nitrobenzanthrone (3-NBA)	As above	NQO	Nitroreduction to hydroxylamine *, **	[86,87]
3-Nitrobenzanthrone (3-NBA)	As above	SULT1A1	*O*-Sulfation, sulfo-conjugate, after nitroreduction to hydroxylamine, electrophilic nitrenium ion formation*	[81,84,85,87,91]
3-Nitrobenzanthrone (3-NBA)	As above	SULT1A2	*O*-Sulfation, sulfo-conjugate, after nitroreduction to	[85,87]

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			hydroxylamine, electrophilic nitrenium ion formation	
3-Nitrofluoranthene (3-NF)	Constituent of particulate matter in diesel-engine exhaust, urban air pollutants, nitroarene	P450 1B1 (co-expressed with NPR)	1-Aminopyrene formation, nitroreduction/*O*-acetylation, at low concentrations, electrophilic nitrenium ion formation	[9]
4,10-Diazachrysene (4,10-DAC)	Chrysene derivative	P450 1A2	Oxidation, enamine epoxide formation	[11,12]
4,10-Diazachrysene (4,10-DAC)	Chrysenederivative	P450 2A6	Oxidation, enamine epoxide formation	[11,13]
4-Hydroxycyclopenta[*def*]chrysene	Metabolite of cyclopenta[*def*] chrysene, automobile exhaust, and cigarette smoke compound	SULT1B1	*O*-Sulfation, sulfo-conjugate, electrophilic nitrenium ion formation *	[14,15]
4-Hydroxycyclopenta[*def*]chrysene	As above	SULT1E1	*O*-Sulfation, sulfo-conjugate, electrophilic nitrenium ion formation	[14,15,56]
4-Nitropyrene (4-NP)	As above	P450 3A4	Nitroreduction, aminopyrene, 4-hydroxylamine, formation **	[13]
4-Nitropyrene (4-NP)	As above	P450 3A4	Oxidation, ring oxidations *	[13]
5,6-Dimethylchrysene-1,2-diol	Metabolite of 5,6-dimethylchrysene	P450 1A1	Oxidation, diolepoxide formation	[1,25,33,38]

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5,6-Dimethylchrysene-1,2-diol	As above	P450 1A2	Oxidation, diolepoxide formation	[1,33,38]
5,6-Dimethylchrysene-1,2-diol	As above	P450 1B1	Oxidation, diolepoxide formation	[1,3,24,25,33,38,43]
5-Methylchrysene	Environmental pollutants, vehicle emissions, and tobacco smoke compound	P450 1A1	1,2-Dihydrodiol formation (medium Km, high activity, high efficiency), oxidation *	[1,33,49,66,92]
5-Methylchrysene	As above	P450 1A2	1,2-Dihydrodiol formation, oxidation	[1,33,92]
5-Methylchrysene	As above	P450 1B1	Oxidation, ring oxidation	[43]
5-Methylchrysene	As above	P450 3A4	Oxidation, ring oxidations	[92]
5-Methylchrysene	As above	P450 2C10	1,2-Dihydrodiol formation, oxidation	[92]
5-Methylchrysene-1,2-diol	Metabolite of 5-methylchrysene	AKR1A1	Oxidation, o-quinone formation (medium Km, high activity, high efficiency)	[38,47,48]
5-Methylchrysene-1,2-diol	As above	P450 1A1	Oxidation, *o*-quinone formation	[1,24,25,33,38,66]
5-Methylchrysene-1,2-diol	As above	P450 1A2	Oxidation, *o*-quinone formation	[1,24,33,38]
5-Methylchrysene-1,2-diol	As above	P450 1B1	Oxidation (medium Km, high activity, high efficiency, *o*-quinone formation *	[1,3,24,25,33,38,41,43,66]
5-Methylchrysene-1,2-diol	As above	P450 2W1	Oxidation, *o*-quinone formation	[43]
5-Methylchrysene-7,8-diol	As above	AKR1C1	Oxidation, *o*-quinone formation	[18,19]

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5-Methylchrysene-7,8-diol	As above	AKR1C2	Oxidation, *o*-quinone formation	[19]
5-Methylchrysene-7,8-diol	As above	AKR1C3	Oxidation, *o*-quinone formation	[19]
5-Methylchrysene-7,8-diol	As above	AKR1C4	Oxidation, *o*-quinone formation**	[19]
5-Nitroacenaphthene	Environmental pollutants, industrial and research chemicals, acenaphthene derivative, nitroarene	SULT1A1	O-Sulfation, sulfo-conjugation, electrophilic nitrenium ion formation * (after nitroreduction)	[81]
6-Aminochrysene (6-AC)	Metabolite of 6-nitrochrysene, arylamine	P450 1A1	Oxidation (high activity) *	[1,3,24]
6-Aminochrysene (6-AC)	As above	P450 1A2	Oxidation	[3,24,57–59,93,94]
6-Aminochrysene (6-AC)	As above	P450 1B1	Oxidation *	[1,24]
6-Aminochrysene (6-AC)	As above	P450 2A6	Oxidation	[95]
6-Aminochrysene (6-AC)	As above	P450 2B6	Oxidation	[93,96]
6-Aminochrysene (6-AC)	As above	P450 3A4	Oxidation, ring oxidation **	[52,73,89,93,94]
6-Aminochrysene (6-AC)	As above	NAT2	*O*-Acetylation after N-hydroxylation, electrophilic nitrenium ion formation	[53]
6-Aminochrysene (6-AC)	As above	P450 3A7	Oxidation, ring oxidation	[73]
6-Aminochrysene-1,2-diol	As above	P450 1A1	Diol epoxide formation, oxidation	[24,93,94]
6-Aminochrysene-1,2-diol	As above	P450 1A2	Diol epoxide formation, oxidation	[24,93,94]

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6-Aminochrysene-1,2-diol	As above	P450 1B1	Diol epoxide formation, oxidation *	[24,93,94]
6-Aminochrysene-1,2-diol	As above	P450 3A4	Diol epoxide formation, oxidation	[93,94]
6-Hydroxymethylanthracene	Metabolite of methylanthracene, research chemicals, benzylic alcohol	SULT1C3	*O*-Sulfation, sulfo-conjugate formation, electrophilic nitrenium ion formation *	[46]
6-Hydroxymethylbenzo[*a*]pyrene	Metabolite of methylbenzo[a]pyrene, research chemicals, PAH derivative	SULT1B1	*O*-Sulfation, sulfo-conjugate formation, electrophilic nitrenium ion formation *	[15]
6-Hydroxymethylbenzo[*a*]pyrene	As above	SULT1C3	*O*-Sulfation, sulfo-conjugate formation, electrophilic nitrenium ion formation *	[46]
6-Hydroxymethylbenzo[*a*]pyrene	As above	SULT2A1	*O*-Sulfation, sulfo-conjugate formation, electrophilic nitrenium ion formation *	[14,15]
6-Methylchrysene	Environmental pollutants, tobacco smoke constituent	P450 1A1	1,2-Dihydrodiol formation, oxidation **	[92]
6-Methylchrysene	As above	P450 1A2	1,2-Dihydrodiol formation, oxidation	[92]
6-Methylchrysene	As above	P450 2C10	1,2-Dihydrodiol formation, oxidation	[92]
6-Methylchrysene	As above	P450 1A2	6-Methylhydroxylation, oxidation	[92]

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6-Methylchrysene	As above	P450 3A4	6-Methylhydroxylation, oxidation	[92]
6-Nitrochrysene	Environmental pollutants, research chemicals, nitroarene	P450 1A2	Oxidation, *trans*-1,2-dihydro-1,2-dihydroxy-6-nitrochrysene formation *	[1,50]
6-Nitrochrysene	As above	P450 1A1	Oxidation, *trans*-1,2-dihydro-1,2-dihydroxy-6-nitrochrysene formation *	[1,50]
6-Nitrochrysene	As above	P450 3A4	Nitroreduction, 6-amino chrysene formation *	[1,50]
7,12-Dimethylbenz[*a*]anthracene (7,12-DMBA)	Product of incomplete combustion product of gasoline and coal	P450 1A1	Oxidation (low Km, high activity and efficiency) *	[1,25,33,97,98]
7,12-Dimethylbenz[*a*]anthracene (7,12-DMBA)	As above	P450 1A2	Oxidation	[1,33,98]
7,12-Dimethylbenz[*a*]anthracene (7,12-DMBA)	As above	P450 1B1	Oxidation (low Km, high activity, and efficiency)	[1,25,33,43,98]
7,12-Dimethylbenz[*a*]anthracene (7,12-DMBA)	As above	P450 2C9	Oxidation	[1,33,97]
7,12-Dimethylbenz[*a*]anthracene (7,12-DMBA)	As above	P450 2D6	Oxidation	[97]
7,12-Dimethylbenz[*a*]anthracene (7,12-DMBA)	Metabolite of 7,12-DMBA	AKR1A1	Oxidation, *o*-quinone formation	[47,48]
7,12-Dimethylbenz[*a*]anthracene (7,12-DMBA)	As above	AKR1C2	Oxidation, *o*-quinone formation	[19]

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7,12-Dimethylbenz[*a*]anthracene (7,12-DMBA)	As above	AKR1B10	Oxidation, *o*-quinone formation	[16]
7,12-Dimethylbenz[*a*]anthracene (7,12-DMBA)	As above	AKR1C1	Oxidation, *o*-quinone formation, minor enzyme	[18,19]
7,12-Dimethylbenz[*a*]anthracene (7,12-DMBA)	As above	AKR1C3	Oxidation, *o*-quinone formation	[19]
7,12-Dimethylbenz[*a*]anthracene (7,12-DMBA)	As above	AKR1C4	Oxidation, *o*-quinone formation **	[19]
7,12-Dimethylbenz[*a*]anthracene (7,12-DMBA)	As above	P450 1A1	3,4-Dihydrodiol-1,2-epoxide formation (medium Km, high activity, high efficiency), oxidation*, also, micronucleus frequency increased in CHL-A1 cells	[1,3,25,33,38,90]
7,12-Dimethylbenz[*a*]anthracene (7,12-DMBA)	As above	P450 1A2	Oxidation	[1,33,38]
7,12-Dimethylbenz[*a*]anthracene (7,12-DMBA)	As above	P450 1B1	3,4-Dihydrodiol-1,2-epoxide formation (medium Km, high activity, high efficiency), oxidation *	[1,3,24,25,33,38]
7-Hydroxy-12-methylbenz[*a*]anthracene	Metabolite of DMBA	SULT2A1	*O*-Sulfation, sulfo-conjugate formation, electrophilic nitrenium ion formation *	[55]
7-Hydroxy-7,8,9,10-tetrahydrobenzo[*a*]pyrene	Metabolite of B[a]P	SULT1A1	*O*-Sulfation, sulfo-conjugate formation, electrophilic nitrenium ion formation*	[55. 56]

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7-Hydroxy-7,8,9,10-tetrahydrobenzo[*a*]pyrene	As above	SULT1E1	*O*-Sulfation, sulfo-conjugate, electrophilic nitrenium ion formation *	[56]
7-Methylbenz[*a*]anthracene-3,4-diol	Metabolite of 7-methylbenz*[a]*anthracene	AKR1A1	Oxidation, *o*-quinone formation, preferential for (-)-3*S*,4*S*-oxidation	[47,48]
7-Methylbenz[*a*]anthracene-3,4-diol	As above	AKR1C1	Oxidation, *o*-quinone formation, minor enzyme	[19]
7-Methylbenz[*a*]anthracene-3,4-diol	As above	AKR1C2	Oxidation, *o*-quinone formation	[19]
7-Methylbenz[*a*]anthracene-3,4-diol	As above	AKR1C3	Oxidation, *o*-quinone formation	[19]
7-Methylbenz[*a*]anthracene-3,4-diol	As above	AKR1C4	Oxidation, *o*-quinone formation	[19]
7-Methylbenz[*c*]acridine (7MBAC)	Research chemicals, aza-aromatic	P450 1A2	3,4-Dihydrodiol formation, oxidation	[100]
7-Methylbenz[*c*]acridine (7MBAC)	As above	P450 1A1	K-region oxide formation, oxidation *	[100]
7-Methylbenz[*c*]acridine (7MBAC)	As above	P450 1A2	K-region oxide formation, oxidation	[100]
7-Methylbenz[*c*]acridine (7MBAC)	As above	P450 3A4	K-region oxide formation, oxidation	[100]
9-Hydroxybenzo[*a*]pyrene	Metabolite of B[*a*]P	P450 1A1	Oxidation	[1]
9-Hydroxybenzo[*a*]pyrene	As above	P450 1B1	Oxidation	[1]
9-Hydroxymethyl-10-methylanthracene	Industrial and research	SULT2A1	*O*-Sulfation, sulfo-conjugate,	[56]

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	chemicals, used in the synthesis of fluorescent dyes and pigments		electrophilic nitrenium ion formation	
9-Hydroxymethylanthracene	Research chemical	SULT2A1	*O*-Sulfation, sulfo-conjugate, electrophilic nitrenium ion formation	[56]
Benz[*a*]anthracene	Incomplete combustion products of organic matter, found in gasoline and diesel fuel exhaust, tobacco smoke compound	P450 1A1	Oxidation	[1,33]
Benz[*a*]anthracene-1,2-diol	Metabolite of benz[*a*]anthracene	P450 1A1	Oxidation, micronucleus frequency increased in CHL-A1 cells	[1,38,90,101]
Benz[*a*]anthracene-3,4-diol	As above	AKR1A1	Oxidation, *o*-quinone formation	[47,48]
Benz[*a*]anthracene-3,4-diol	As above	AKR1C1	Oxidation, *o*-quinone formation	[19]
Benz[*a*]anthracene-3,4-diol	As above	AKR1C2	Oxidation, *o*-quinone formation	[19]
Benz[*a*]anthracene-3,4-diol	As above	AKR1C3	Oxidation, *o*-quinone formation	[19]
Benz[*a*]anthracene-3,4-diol	As above	AKR1C4	Oxidation, *o*-quinone formation	[19]
Benz[*a*]anthracene-3,4-diol	As above	P450 1A1	Oxidation	[1,33]
Benz[*a*]anthracene-3,4-diol	As above	P450 1A2	Oxidation	[1,33]

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Benz[*a*]anthracene-5,6-diol	As above	P450 1A1	Oxidation	[1,38]
Benzo[*a*]perylene	Incomplete combustion products present in automobile exhaust, tobacco smoke, grilled meat, edible oil compound	P450 1A1	Oxidation	[102]
Benzo[*a*]pyrene (B[*a*]P)	Incomplete combustion product of organic matter, coal tar, tobacco smoke, and many foods (e.g., grilled meat) compound	P450 1A1	*trans*-7,8-Dihydroxy-9,10-epoxy-7,8,9,10-tetrahydro- formation (low activity, medium activity, or high activity, high efficiency), 1,6-,3,6-,6,12-dione (quinone formation, low activity), oxidation *	[1,24,27,28,30–33,52,67,103,105–108]
Benzo[*a*]pyrene (B[*a*]P)	As above	P450 1B1	*trans*-7,8-Dihydroxy-9,10-epoxy-7,8,9,10-tetrahydro- formation (medium Km, high activity, high efficiency), 1,6-,3,6-Dione (quinone formation, low activity), oxidation **	[1,24–27,33,38,43,44,70,102,104,109,129]
Benzo[*a*]pyrene-7,8-oxide (B[*a*]P-7,8-oxide)	Metabolite of B[*a*]P	Epoxide hydrolase, EH	Hydrolysis to B[*a*]P-7,8-diol, participation in B[*a*]P toxicity	[1,27]
Benzo[*b*]fluoroanthene-9,10-diol (B[*b*]F-11,12-diol)	Metabolite of B[*b*]F	P450 1A1	Oxidation *	[1,3,24,25,33,38]

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Benzo[*b*]fluoroanthene-9,10-diol (B[*b*]F-11,12-diol)	As above	P450 1A2	Oxidation	[1,24,33,38]
Benzo[*b*]fluoroanthene-9,10-diol (B[*b*]F-11,12-diol)	As above	P450 1B1	Oxidation	[1,24,25,33,38]
Benzo[*c*]phenanthrene (B[*c*]P)	Wood and fossil fuel exhaust compound	P450 1A1	Dihydrodiol 3,4-, 1,2-epoxide formation, oxidation **	[106]
Benzo[*c*]phenanthrene (B[*c*]P)	As above	P450 1B1	Dihydrodiol 3,4-, 1,2-epoxide formation, oxidation **	[1,25,33,110–112]
Benzo[*c*]phenanthrene (B[*c*]P)	As above	P450 2C9	Oxidation	[33]
Benzo[*c*]phenanthrene-3,4-dio (B[*c*]P-3,4-diol)	Metabolite of B[*c*]P	AKR1C2	Oxidation, *o*-quinone formation	[19]
Benzo[*c*]phenanthrene-3,4-dio (B[*c*]P-3,4-diol)	As above	AKR1C4	Oxidation, *o*-quinone formation	[19]
Benzo[*c*]phenanthrene-3,4-dio (B[*c*]P-3,4-diol)	As above	P450 1A2	Oxidation	[1]
Benzo[*c*]phenanthrene-3,4-dio (B[*c*]P-3,4-diol)	As above	AKR1C3	Oxidation, *o*-quinone formation	[19]
Benzo[*g*]chrysene-11,12-diol (B[*g*]C-11,12-diol)	Metabolite of B[*g*]C, fossil fuels and organic materials incomplete combustion product	P450 1A1	Oxidation	[1,25,33,38]
Benzo[*g*]chrysene-11,12-diol (B[*g*]C-11,12-diol)	As above	AKR1C1	Oxidation, *o*-quinone formation	[18,19]
Benzo[*g*]chrysene-11,12-diol (B[*g*]C-11,12-diol)	As above	AKR1C2	Oxidation, *o*-quinone formation	[19]

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Benzo[*g*]chrysene-11,12-diol (B[*g*]C-11,12-diol)	As above	AKR1C3	Oxidation, *o*-quinone formation	[19]
Benzo[*g*]chrysene-11,12-diol (B[*g*]C-11,12-diol)	As above	AKR1C4	Oxidation, *o*-quinone formation **	[19]
Benzo[*g*]chrysene-11,12-diol (B[*g*]C-11,12-diol)	As above	P450 1A2	Oxidation	[1,33,38]
Benzo[*g*]chrysene-11,12-diol (B[*g*]C-11,12-diol)	As above	P450 1B1	Oxidation *	[1,3,24,25,33,38]
Chrysene-1,2-diol	As above	AKR1C2	Oxidation, *o*-quinone formation	[19]
Chrysene-1,2-diol	As above	AKR1C3	Oxidation, *o*-quinone formation	[19]
Chrysene-1,2-diol	As above	AKR1C4	Oxidation, *o*-quinone formation	[19]
Chrysene-1,2-diol	As above	P450 1A1	Oxidation *	[1,25,33]
Chrysene-1,2-diol	As above	P450 1A2	Oxidation	[1,33,38]
Chrysene-1,2-diol	As above	P450 1B1	Oxidation, diolepoxide formation *	[1,3,24,25,33,38,43]
Chrysene-1,2-diol	As above	P450 2W1	Oxidation, diolepoxide formation	[43]
Cyclopenta[*c,d*]pyrene	As above	P450 1B1	Oxidation	[113]
Cyclopenta[*c,d*]pyrene	Incomplete combustion product of organic matter, gasoline engine exhaust compound	P450 1A1	Oxidation	[106]

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Dibenz[*a,h*]acridine	Incomplete combustion product of organic substances, primarily found in gasoline exhaust, petroleum refinery incinerator emissions, coal combustion emissions, cigarette smoke, and coal tar pitch	P450 1A1	10,11-Diol formation, oxidation *	[114]
Dibenz[*a,h*]acridine	As above	P450 1B1	10,11-Diol formation, oxidation	[114]
Dibenz[*a,h*]anthracene	Incomplete combustion product of organic substances found in air, soil, or sediment, and on pyrolysis of tobacco	P450 1A1	Oxidation	[1]
Dibenz[*a,h*]anthracene	As above	P450 1A2	1,2-Dihydrodiol formation, oxidation **	[115]
Dibenz[*a,h*]anthracene	As above	P450 1A2	*trans*-3,4-Dihydrodiol formation, oxidation	[115]
Dibenz[*a,h*]anthracene	As above	P450 2B6	*trans*-3,4-Dihydrodiol formation, oxidation	[115]
Dibenz[*a,h*]anthracene	As above	P450 2C9	*trans*-3,4-Dihydrodiol formation, oxidation **	[115]

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Dibenz[*a,j*]acridine (DBJAC)	Automobile exhaust, coal burning, incinerator waste streams, cigarette smoke compound, heteroarene	P450 3A4	3,4-Dihydrodiol formation, oxidation *	[100]
Dibenz[*a,j*]acridine (DBJAC)	As above	P450 1A1	*K*-region oxide formation, oxidation	[100]
Dibenz[*a,j*]acridine (DBJAC)	As above	P450 1A2	*K*-region oxide formation, oxidation	[100]
Dibenz[*a,j*]acridine (DBJAC)	As above	P450 1A1	*K*-region dihydrodiol formation	[100]
Dibenz[*a,j*]acridine (DBJAC)	As above	P450 1A1	3,4-Dihydrodiol formation, oxidation	[100]
Dibenz[*a,j*]acridine (DBJAC)	As above	P450 1A2	3,4-Dihydrodiol formation, oxidation	[100]
Dibenz[*a,j*]acridine (DBJAC)	As above	P450 3A5	3,4-Dihydrodiol formation, oxidation	[100]
Dibenz[*a,j*]acridine (DBJAC)	As above	P450 1A2	*K*-region dihydrodiol formation, oxidation	[100]
Dibenzo[*a,e*]fluoranthene	Research chemical	P450 1A1	Oxidation, mutagenicity	[102]
Dibenzo[*a,e*]pyrene (DB[*a,e*]P)	Tobacco smoke compound	P450 1A1	Oxidation, mutagenicity	[102]
Dibenzo[*a,f*]fluoranthene	Incomplete combustion of organic materials, such as fossil fuels, wood, and tobacco smoke compound	P450 1A1	Oxidation, mutagenicity	[102]

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Dibenzo[*a*,*h*]pyrene (DB[*a*,*h*]P)	Tobacco smoke compound	P450 1A1	Oxidation, mutagenicity	[102]
Dibenzo[*a*,*k*]fluoranthene	Incomplete burning of coal, oil, gas, wood, garbage, and other organic substances compound	P450 1A1	Oxidation, mutagenicity	[102]
Dibenzo[*a*,*l*]pyrene (DB[*a*,*l*]P)	Combustion of wood and coal, gasoline and diesel exhaust, and tobacco smoke compound	P450 1A1	(-)-*syn*- and (-)-*anti*-11,12-Dihydrodiol-13,14-epoxide formation (medium Km, high activity, high efficiency, oxidation *	[1,28,33,102,116–123]
Dibenzo[*a*,*l*]pyrene (DB[*a*,*l*]P)	As above	P450 1A2	(-)-*anti*-11,12-Dihydrodiol-13,14-epoxide formation, oxidation	[33,119,120]
Dibenzo[*a*,*l*]pyrene (DB[*a*,*l*]P)	As above	P450 1B1	(-)-*anti*-11,12-Dihydrodiol-13,14-epoxide formation (medium Km, high activity, high efficiency), oxidation *	[1,28,33,43,44,116–123,128]

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Dibenzo[*a,l*]pyrene-11,12-diol (DB[*a,l*] - 11,12-diol)	Metabolite of DB[*a,l*]P	P450 1A1	11,12-Dihydrodiol-13,14-epoxide formation (medium Km, high activity, high efficiency, oxidation *	[1,25,28,33,38,41,104,116–118,123]
Dibenzo[*a,l*]pyrene-11,12-diol (DB[*a,l*] - 11,12-diol)	As above	P450 1A2	Oxidation	[31,38,104]
Dibenzo[*a,l*]pyrene-11,12-diol (DB[*a,l*] - 11,12-diol)	As above	P450 1B1	11,12-Dihydrodiol-13,14-epoxide formation (medium Km, high activity, high efficiency), oxidation *	[1,24,25,28,33,38,41,43,44, 104,116–118,123]
Dibenzo[*a,l*]pyrene-11,12-diol (DB[*a,l*] - 11,12-diol)	As above	P450 2W1	Oxidation, diolepoxide formation	[43]
Dibenzo[*b,k*]fluoranthene	Environmental pollutants, diesel fuel particulate compound	P450 1A1	Oxidation, mutagenicity	[102]
Fluoranthene-2,3-diol	Metabolite of fluoranthene	P450 1A1	Oxidation, diolepoxide formation	[1,38]
Naphthalene	As above	P450 2F1	Oxidation	[124]
Naphthalene 1,2-diol	Metabolite of naphthalene	AKR1C1	Oxidation, *o*-quinone formation **	[18,19]
Naphthalene 1,2-diol	As above	AKR1C2	Oxidation, *o*-quinone formation **	[19]
Naphthalene 1,2-diol	As above	AKR1C3	Oxidation, *o*-quinone formation	[19]
Naphthalene 1,2-diol	As above	AKR1C4	Oxidation, *o*-quinone formation	[19]
Naphtho[1,2-*k*]fluoranthene	Environmental pollutants, incomplete combustion of	P450 1A1	Oxidation, mutagenicity	[102]

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	organic matter compound			
Naphtho[2,3-*a*]pyrene	Air pollutants, applied in biological and electronic fields, incomplete combustion processes, and tobacco smoke compound	P450 1A1	Oxidation, mutagenicity	[102]
Naphtho[2,3-*e*]pyrene	As above	P450 1A1	Oxidation, mutagenicity	[102]
N-Hydroxy-2-acetylaminofluorene	Metabolite of 2-acetylaminofluorene, hydroxamic acid, heterocyclic amine	SULT1A1	*O*-Sulfation, sulfo-conjugate formation, electrophilic nitrenium ion formation	[14,15]
N-Hydroxy-2-acetylaminofluorene	As above	SULT1A2	O-Sulfation, sulfo-conjugate formation, electrophilic nitrenium ion formation *	[14,15,63]
N-Hydroxy-2-aminofluorene	Metabolite of 2-aminofluorene, hydroxamic acid, heterocyclic amine	NAT1	*O*-Acetylation, electrophilic nitrenium ion formation	[130]
N-Hydroxy-2-aminofluorene	As above	NAT2	*O*-Acetylation, electrophilic nitrenium ion formation	[130]
N-Hydroxy-2-aminofluorene	As above	SULT1A1	*O*-Sulfation, sulfo-conjugate, electrophilic	[14,125]

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			nitrenium ion formation	
N-Hydroxy-2-aminofluorene	As above	SULT1A2	*O*-Sulfation, sulfo-conjugate formation, electrophilic nitrenium ion formation *	[81]
Phenanthrene	Environmental contaminants, industrial chemicals, tobacco smoke compound	P450 1A1	Oxidation to 1,2- (major reaction), 9,10- and 3,4-dihydrodiols (minor reactions) and phenols, at high concentration	[126]
Phenanthrene	As above	P450 1A2	Oxidation to 1,2- (major reaction), 3,4-, 9,10-dihydrodiols and phenols	[126]

* Potent toxification, ** Major enzyme.

Included are reactions and products that are not toxic but as substrates in additional reactions products or intermediates formed exert toxicity (e.g., products of hydroxylation reactions catalyzed by P450 enzymes and products of hydrolysis reactions).

Abbreviations for the enzyme names used in the text and Tables are explained in Table 1. The data presented in Table 2 are used for calculations presented in Figures. The enzymes, described as minor participating enzymes, participate in the toxication reactions with less than 5% of the data each.

2. Metabolic Toxication of PAHs

Depending on the structural properties of the compounds and the enzymes involved, the PAHs participate predominantly as substrates in oxidations (participating at 67% of the reactions) involving C and N atoms (Figure 1).

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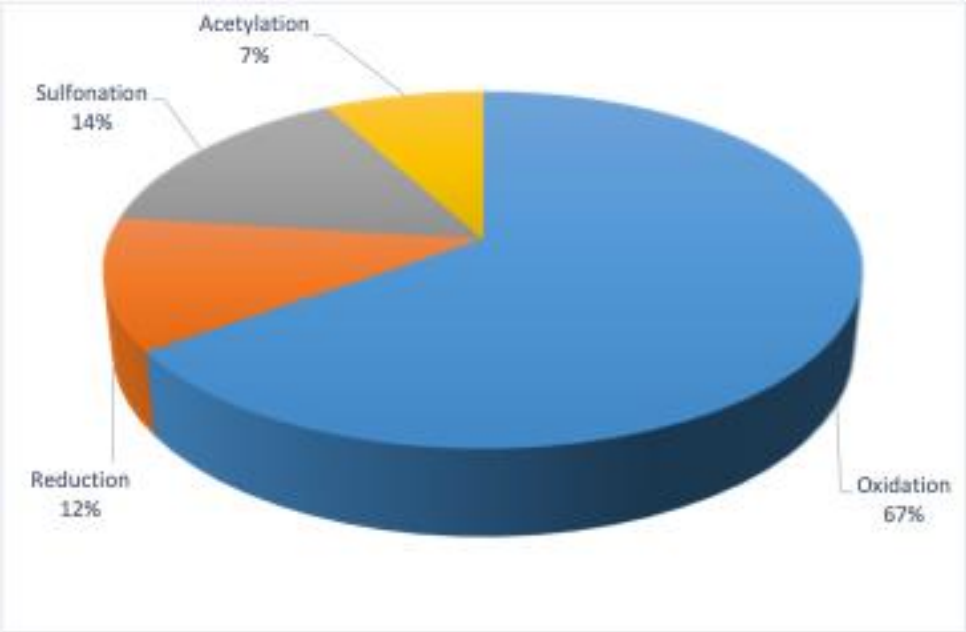

Figure 1. The participation of metabolic reactions in the toxication of PAHs and metabolites catalyzed by human metabolizing enzymes (calculated on 290 records).

Table 2 includes suggested or proposed toxic species such as electrophilic nitrenium ion formation following *O*-sulfation or *O*-acetylation reactions. The oxidation reactions involve the formation of dihydrodiols, epoxides, and dihydrodiol epoxides (all catalyzed by P450 enzymes), and quinones (catalyzed by AKR and P450 enzymes), with a minor contribution of COX enzymes. Reactions of *N*-oxidations are catalyzed by P450, LPO, MPO, and PGHS enzymes. In some examples, e.g., the formation of quinones, the reaction is selective to the substrate configuration. For instance, oxidation of 7-methylbenz[*a*]anthracene-3,4-diol is preferential for (-)-3*S*,4*S*-, and that of (+)-benzo[*a*]pyrene-7,8-dihydrodiol is preferential for (-)-7*R*,8*R*-oxidation (Table 2). The significance of the formation of *o*-quinones and other reactive oxygen species for the metabolism and toxicity of different chemicals (e.g., carcinogens and drugs) has been discussed previously [6,8]. Reductive reactions participate at 12% in the toxication of the PAHs with prevailing nitro-reductions to amino groups. Of other reactions, *O*-sulfations participated at 14%, and *O*-acetylations at 7% (Figure 1). The data also show that depending on the toxicant structure, acetylation, and sulfation reactions in some examples occur after previous reduction by NPR enzyme followed by oxidation. Examples are the *O*-acetylation (catalyzed by NAT enzymes) and *O*-sulfation (catalyzed by SULT enzymes) of 2-nitrofluorene, 2- and 3-nitrobenzanthrone (3-NBA), and other nitro-PAHs. The 3-nitrobenzanthrone is, for instance, toxified by reduction of the nitro to the amino group and consequent *N*-oxidation, or by *N*-sulfation and *N*-acetylation which resulted in the formation of the DNA adducts. It was suggested that P450, PO, NAT, and SULT enzymes may play an important role in the metabolism of 3-NABA and its metabolites to reactive species forming DNA adducts, participating in the genotoxicity of the compounds (Figure 2, Table 2 and references therein).

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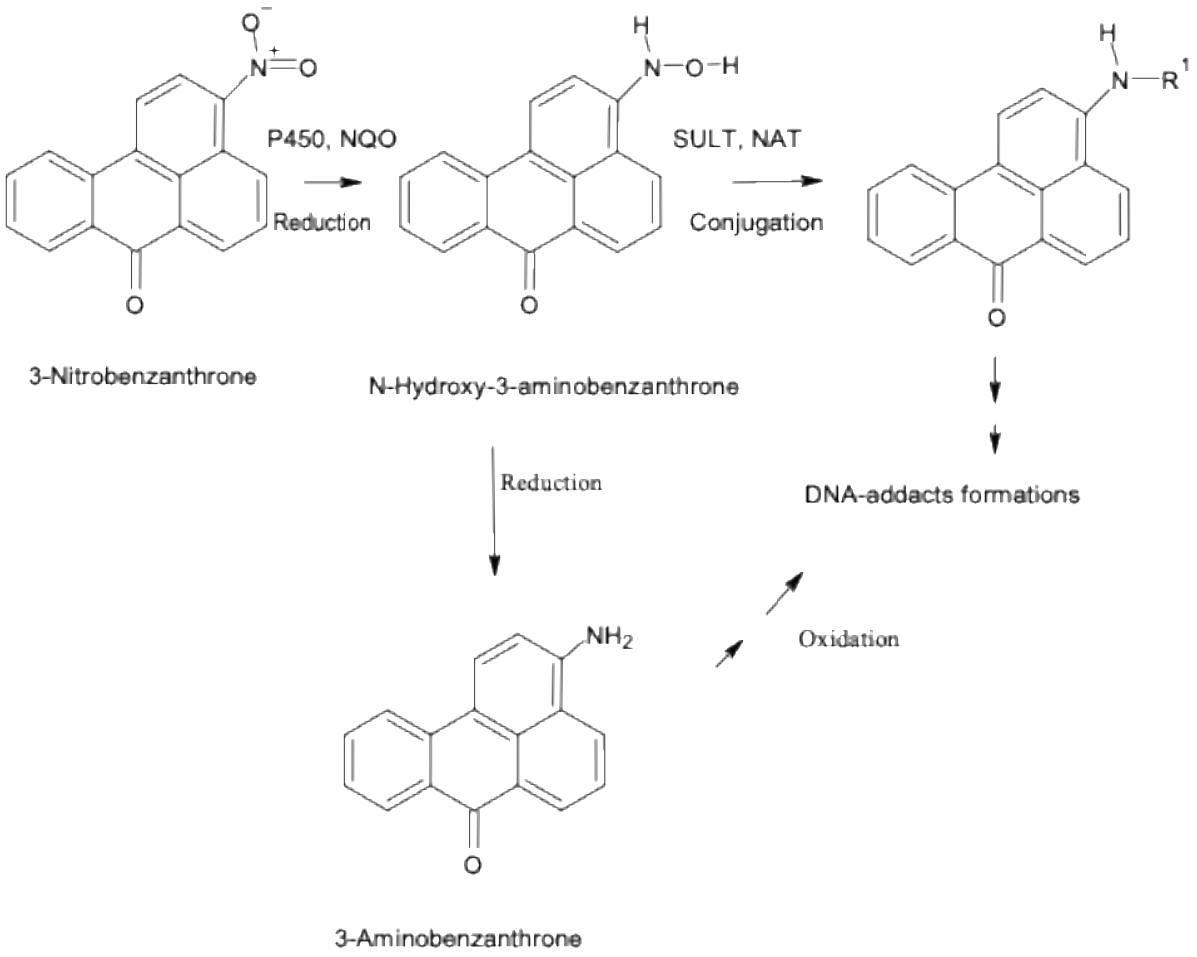

Figure 2. Toxication reactions of 3-nitrobenzanthrone (3-NBA) by human metabolizing enzymes enzymes.

1-Nitropyrene, as well as dinitropyrene derivatives, were suggested to be activated by the catalytic activity of P450 1B1 and 1A2 enzymes by nitroreduction to aminopyrene and subsequent *N*-hydroxylation, which after acetylation would yield a nitrenium ion forming DNA adducts (Table 2 and references therein). Thus, human P450 enzymes were suggested to have activities for both ring oxidations and reductions of nitropyrenes followed by *O*-acetylation/*O*-sulfation and binding to DNA [9,10] (Table 2). Additional examples of toxication by conjugation reactions are reactions of hydroxylated metabolites of methyl- and ethylpyrene, which exert toxic activity after sulfation by SULT enzymes' catalytic activity (Table 2 and references therein).

3. Enzymes

The calculated participation of human metabolizing enzymes in the toxication of the PAHs and their metabolites (Table 2) shows the dominant involvement of P450 enzymes (58%), followed by AKR (16%), SULT (15%), NPR (3%), NAT (6%) and a group of minor participating enzymes composed of LPO, MPO, PGHS, NQO1, XOR, and COX, which participate to the extent of 3% (Fig. 3, Table 2).

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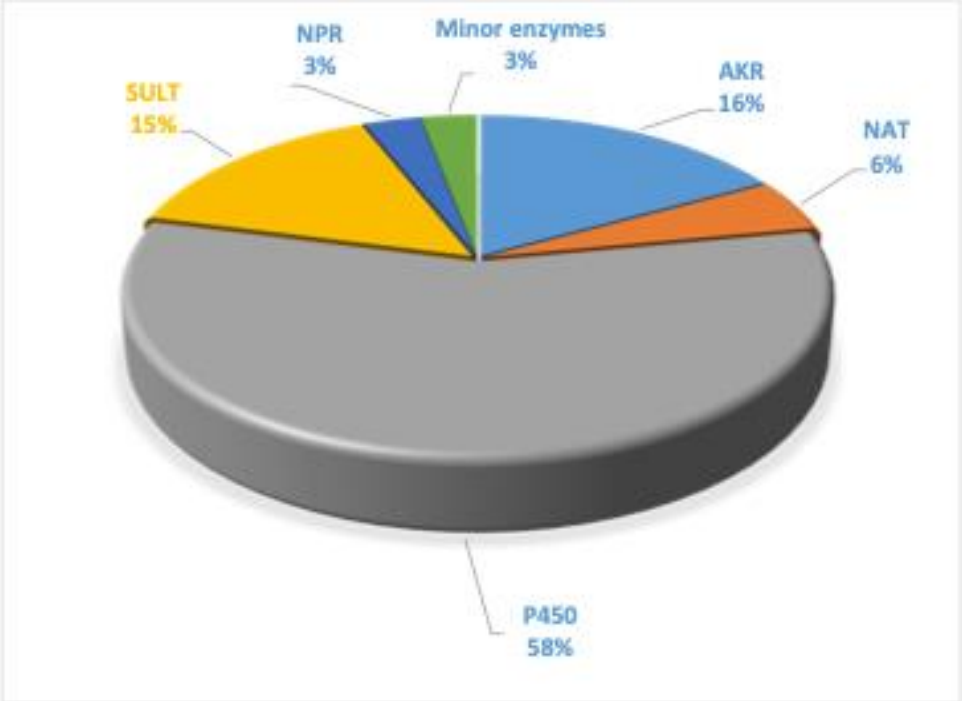

Figure 3. The participation of human metabolizing enzymes in the toxication of PAHs and metabolites (data calculated on 98 compounds).

For comparison, considering the toxication of drugs, the dominant role of P450 enzymes was also recorded, but to an extent at 72%. The differences between the toxication of drugs and PAHs are also recorded in the composition of a group of minor participating enzymes which is in the case of drug toxication composed of AADAC, ADH, CAT, CES, COX, NPR, LPO, HB + H_2O_2) [8].

4. P450 Enzymes

The analysis showed the dominant role of P450 Family 1 (P450 1A1, 1A2, and 1B1) in the toxication of PAHs participating collectively at 75% of the reactions with domination of P450 1A1 enzyme (at 32%). The contribution of other P450 enzymes was 3A4 (8%) and 2W1 (4%). The group of minor participating enzymes which is composed of P450s 2B6, 2C9, 2C10, 2D6, 2E1, 2F1, 3A5, 3A7, and 4B1, participated altogether at 13% (Figure 4).

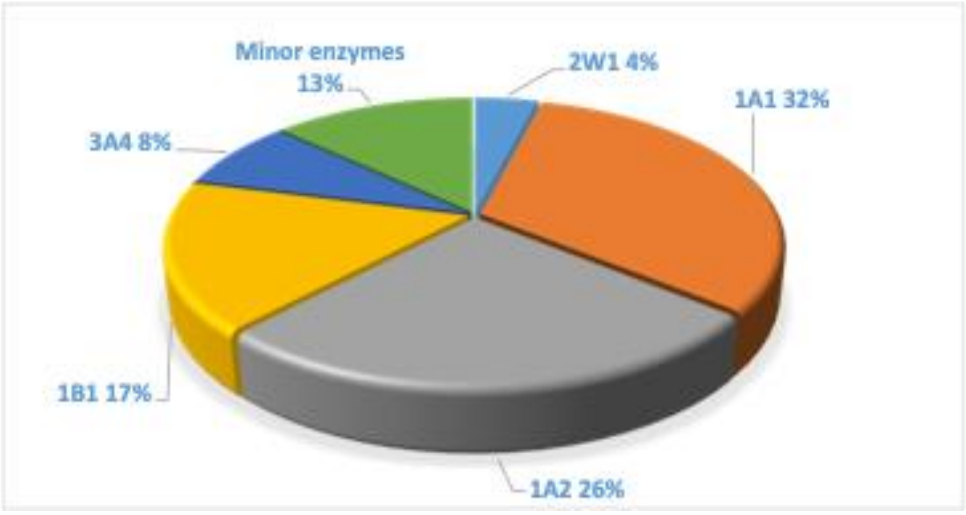

Figure 4. The participation of human P450 enzymes in the toxication of PAHs and metabolites (data calculated on 98 compounds).

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In the previous analysis on the toxication of general carcinogenic chemicals the dominant role of P450 enzymes was also shown to participate in 66% of the reactions, as well as the dominant participation of cytochrome P450 Family 1 (P450 1A1, 1A2, and 1B1) participating with 58%. P450 3A4 enzyme participated in the toxication of general carcinogens with 10% [4] comparably to the present analysis with participation at 8% (Figure 4). These results show the dominant role of P450 enzymes in the toxication of both PAHs and general carcinogens for the compounds taken into analysis.

5. Effect of the Structure of PAHs on the Toxication Reactions

To analyze the effects of the structure composition of the PAHs analyzed (Table 2) on the toxification reactions, participating enzymes, and metabolites formed, the data were divided into those that relate to the compounds with *C*-atoms (*C*-PAHs, 64 compounds), and to those with *C*- and *N*-atoms (*N*-PAHs, 34 compounds) in the structure. An example of the *C*-PAH compound toxication presented is the role of P450, AKR, COX, SULT, and EH enzymes in the metabolic toxication of benzo[*a*]pyrene (Figure 5).

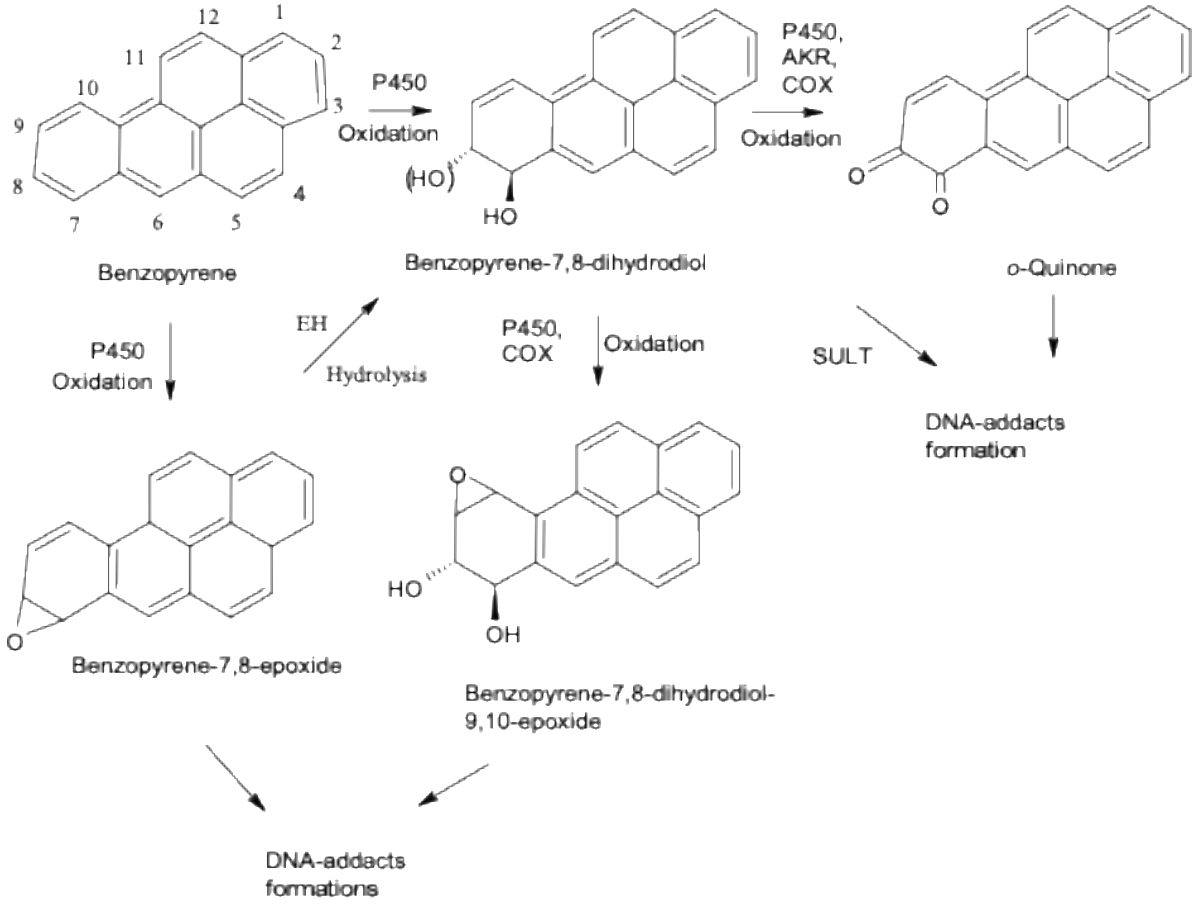

Figure 5. Toxication reactions of benzo[*a*]pyrene (B[*a*]P) by human metabolizing enzymes.

The reactions include oxidative reactions e.g., hydroxylation, epoxidation, hydrolysis to dihydrodiols, *o*-quinone formation, and sulfoconjugation. The properties of benzo[*a*]pyrene as a substrate and its metabolites in the reactions catalyzed by human P450 enzymes, the factors influencing the reactions, and the kinetic data have been reported before implying that the metabolic pathway of B[*a*]P and its metabolites, is very complex and has been the subject of extensive research by different research teams over time [6], Table 2 and references therein.

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The studies published on the mutagenicity of PAHs showed dependence on the presence and position of the N-atom in the structure of the compound. For example, P450 1A2 contributed to the mutagenicity of 10-azaB*a*P more than the recombinant human P450 1A1 enzyme. It was suggested that the presence of the nitrogen atom in the structure led to P450 1A2 as the major enzyme and not P450 1A1. The P450 1A1 is the major enzyme for oxidation/toxication of B[*a*]P possessing C- atoms and no N-atoms in the structure [6,11] (Table 2 and references therein). Furthermore, the change of the position of the N- atom in the structure of the 1,4- and 1,10-diazachrysene resulted in the change in the enzymes responsible for their mutagenicity, e.g., 1,10-diazachrysene was toxified solely by P450 1A2, while 1,4-diazachrysene by 1A2 and 2A6 enzymes [11,12] (Table 2). In addition, studies on the metabolism of 1-, 2-, and 4-nitropyrene derivatives by human cytochrome P450 enzymes catalyzing oxidative and reductive pathways showed dependence upon the position of the nitro group [13]. The present analysis shows clear distinctions between *C*-PAH and *N*-PAH groups of compounds in both the extent of toxication and in the enzymes that catalyze the reactions. The present results show that the *N*-PAH group of compounds participated in the toxication reactions at 66% (Figure 6) compared to the *C*-PAH group of compounds participating at 51%) (Figure 7).

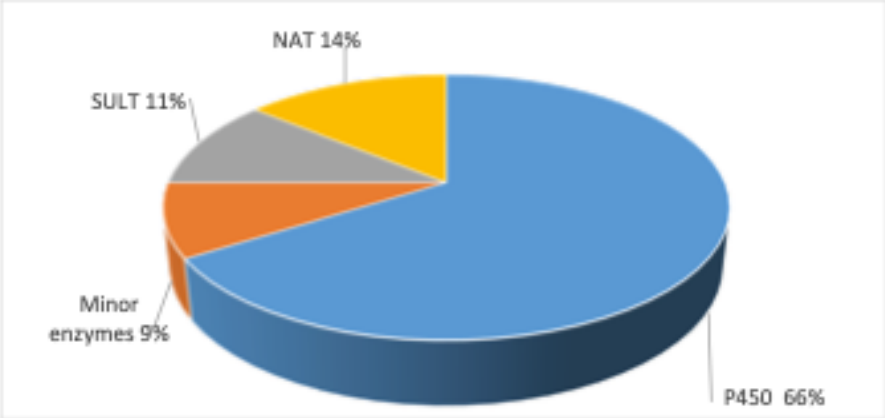

Figure 6. The participation of human metabolizing enzymes in the toxication of *N*-PAHs and metabolites (data calculated on 34 compounds).

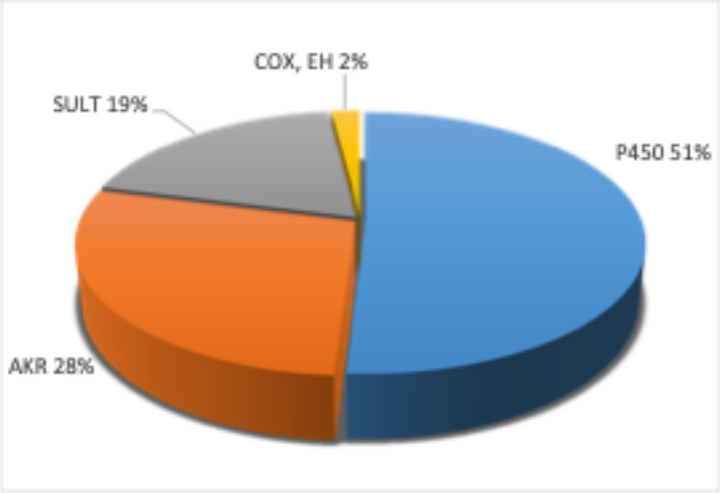

Figure 7. The participation of human metabolizing enzymes in the toxication of *C*-PAHs and metabolites (data calculated on 64 compounds).

It is also shown that the AKR enzymes participated in the activation of *C*-PAHs (at 28%) (Figure 7) and did not participate in the activation of *N*-PAHs (Figure 6). In addition, NAT enzymes participated in the activation of *N*-PAHs (at 14%) (Figure 6), but did not participate in the activation of *C*-PAHs (Figure 7). The differences in the structure of the two groups of compounds have also

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been noticed in the toxication reactions catalyzed by P450 enzymes and the participation of minor participating enzymes. The P450 1A1 enzyme participated at a lower extent in the toxication *N*-PAHs (at 23%) (Figure 8) compared to *C*-PAHs (at 41%) (Figure 9).

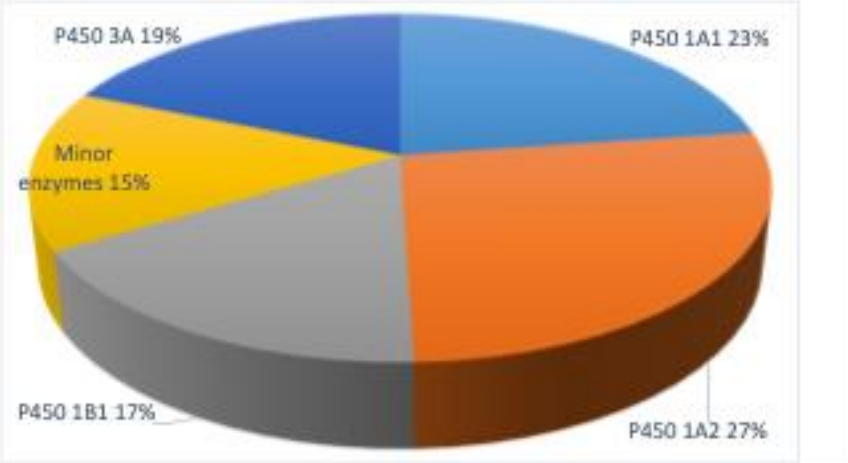

Figure 8. The participation of human P450 enzymes in the toxication of *N*-PAHs and metabolites (data calculated on 34 compounds).

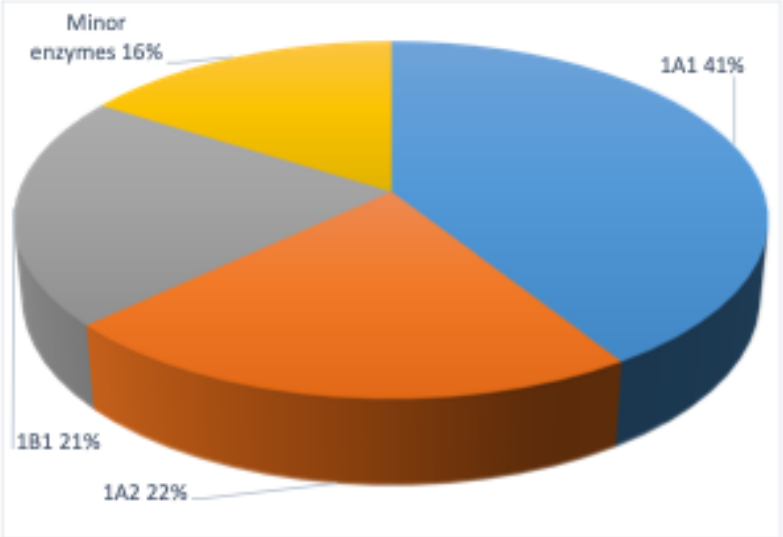

Figure 9. The participation of human P450 enzymes in the toxication of *C*-PAHs and metabolites (data calculated on 64 compounds).

Minor differences are noticed regarding the P4501A2 participation which was at 27% in the group of NPAHs (Figure 8) vs. 22% in the group of *C*-PAHs (Figure 9). The P450 3A4 enzyme is considered a minor participating enzyme in the toxication of the *C*-PAH group of compounds, which participated in the toxication of the *N*-PAH group at 19% (Figure 8). In the *C*-PAH group minor participating enzymes comprise 7 enzymes (P450s 2B6, 2C9, 2C19, 2D6, 2F1, 2W1, and 3A4) participating at 16% (Fig 9). In the *N*-PAH group of compounds the group of minor participating enzymes participated in the toxication reactions with 15% and comprised four enzymes (P450s 2A6, 2B6, 2D6, and 2W1 (Figure 8).

6. Concluding Remarks

Previous analyses of published data on the participation of human metabolizing enzymes in the toxication of drugs showed preferential participation of P450 enzymes with minor involvement of AOX, SULT, FMO, and MPO enzymes [8]. Data analysis on the toxication of carcinogenic chemicals also showed P450 enzymes as the most prominent participating enzymes examined and the

contribution of SULT, NAT, FMO, AKR, and COX enzymes [4]. The predominant contribution of P450 enzymes in catalyzing toxication reactions of chemicals of diverse structures is suggested to be the result of extensive research and the development of affordable methods to be used in research with this group of enzymes [8].

The present paper analyzes data on the toxication of PAHs, constituents of environmental pollutants, by human metabolizing enzymes. Analysed are the effects of the structural characteristics such as the presence of the nitrogen atom in the structure on the participating enzymes and products formed. The results show that oxidation reactions prevail over reductions, sulfation, and acetylation. Of the enzymes, toxications by P450s are revealed as the major enzymes. Within the group of P450 enzymes, the major participation goes to P450 Family 1 (P450s 1A1, 1A2, and 1B1), and of these P450 1A1 participated to the major extent. The analysis of the effect of the chemical structure on the toxications of *C*-PAHs (the compounds that contain *C*-atoms and no *N*-atoms in the structure, vs. *N*-PAH (compounds containing both *C*- and *N*-atoms in the structure) revealed differences between these two groups of compounds in both the extent and the enzymes that catalyze the reactions.

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