Published in final edited form as:
Curr Drug Metab. 2012 July ; 13(6): 787–814.

Summary of Information on the Effects of Ionizing and Non-ionizing Radiation on Cytochrome P450 and Other Drug Metabolizing Enzymes and Transporters

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Abstract

The present paper is an update of data on the effects of ionizing radiation (γ-rays, X-rays, high energy UV, fast neutron) caused by environmental pollution or clinical treatments and the effects of non-ionizing radiation (low energy UV) on the expression and/or activity of drug metabolism (*e.g.*, cytochrome P450,, glutathione transferase), enzymes involved in oxidative stress (*e.g.*, peroxidases, catalase,, aconitase, superoxide dismutase), and transporters. The data are presented in tabular form (Tables 1–3) and are a continuation of previously published summaries on the effects of drugs and other chemicals on cytochrome P450 enzymes (Rendic, S.; Di Carlo, F. *Drug Metab. Rev*., **1997**, *29* (1–2), 413–580, Rendic, S. *Drug Metab. Rev*., **2002**, *34* (1–2), 83–448) and of the data on the effects of diseases and environmental factors on the expression and/or activity of human cytochrome P450 enzymes and transporters (Guengerich, F.P.; Rendic, S. *Curr. Drug Metab.*, **2010**, *11*(1), 1–3, Rendic, S.; Guengerich, F.P. *Curr. Drug Metab.*, **2010**, *11* (1), 4–84). The collective information is as presented by the cited author(s) in cases where several references are cited the latest published information is included. Remarks and conclusions suggesting clinically important impacts are highlighted, followed by discussion of the major findings. The searchable database is available as an Excel file (for information about file availability contact the corresponding author).

Keywords

Ionizing radiation; UV; γ-rays; X-rays; cytochrome P450; CYP; oxidative stress enzymes; transporters; expression; activity

INTRODUCTION

Preparation of this summary was prompted by nuclear plant disasters (Chernobyl (1986), Fukushima (2011)) and the consequent irradiation of humans and other biological systems

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DECLARATION OF INTEREST:
The authors report no financial conflicts of interest.

caused by this environmental pollution. This summary includes also the influence of clinically applied radiation (γ-rays, X-rays, fast neutron) for treatment of specific diseases, as well as the effects of UVA, UVB, and UVC radiation on the activity and/or expression of drug metabolism enzymes such as cytochrome P450 (CYP), which are of prime importance for new drug development and absorption-distribution-metabolism-elimination (ADME) research, the enzymes involved in regulation of oxidative stress (*e.g.*, peroxidases (PO), catalase (CAT), aconitase (ACO), superoxide dismutase (SOD)), and transporters. Ionizing radiation is defined as radiation composed of particles of different energy that can liberate an electron from an atom or molecule. When interacting with organic compounds or other small molecules in the body, ionizing radiation (γ-rays, α- and β-particles, high-frequency ultraviolet, X-rays, and gamma rays, fast neutron irradiation, and contamination with radioactive particles, e.g. uranium or radioactive pollutant contamination), depending on the energy, produces free radicals that can damage tissue molecules. Most UV light is classified as non-ionizing radiation, but the higher energies of the UV spectrum (e.g., ~ 150 nm, or 'vacuum' UV) are ionizing.

Cytochrome P450 enzymes catalyze a number of reactions that have profound effects on the biological activities (therapeutic and/or toxic) of xenobiotics, including drugs, and the significance of the human enzymes in drug metabolism has been reviewed [1–4]. The roles of the transporters, which (depending on the site of expression) may enhance or limit absorption or excretion of drugs and other xenobiotics from an organ or tissue and have additional effects on the biological activities of drugs/xenobiotics, are reviewed elsewhere [5,6]. In addition to a great number of xenobiotics used as drugs or coming from 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 are also of interest [7]. These factors can have profound effects on enzyme activity and expression and therefore also the final biological activity, efficacy, and safety of drugs and other chemicals. A great number of examples from the literature show that the final effect of a drug or other chemical on an organism, whether pharmacological and/or toxicological, depends on regulation of expression and the activity of cytochrome P450 enzymes and transporters. When these properties are changed (resulting in their overexpression or inhibition) by factors such as irradiation (alone or in combination with specific drugs, *e.g.* anticancer drugs) a significant change of therapeutic outcome or resistance to a drug might occur.

Damaging effects of ionizing and UV irradiation result from generation of reactive oxygen species (ROS) and subsequent radical formation and from direct damage to cellular macromolecules, including DNA. The most pronounced effect of prolonged exposure to UV (predominately UVB and UVA) in humans is induction and development of skin cancer. UVB radiation (280–320 nm) is readily absorbed by and can cause severe damage to proteins and DNA. Other UV wavelengths of interest include UVA (320–400 nm), which are less detrimental to skin but still can cause harmful effects. Thus high doses of UVB in the epidermis (and UVA in the dermis) may be responsible for the production of reactive oxygen species [8]. Adverse effects of UV radiation are partially reduced by molecular defense mechanisms including glutathione and enzymes such as superoxide dismutase

(SOD), catalase (CAT), and glutathione peroxidase (GPX), which are involved in quenching excessive levels of ROS and other free radicals [9]. Increased activity of the enzymes protecting against oxidative stress by ionizing or UV irradiation might be beneficial, and decreased activity might enhance damaging effects of irradiation. In addition, modification of the expression and activity of enzymes involved in metabolism (*e.g.*, the toxicologically important CYP2E1 and CYP1 Family enzymes or CYP4A11, which is involved in lipid metabolism) or transporters (*e.g.* the clinically important P-glycoprotein, LRP, or MRP1) can influence the therapeutic outcome or toxicity of other drugs and xenobiotics. In addition, irradiation-induced modification of cytochrome P450 enzyme activity might result in enhanced or diminished formation of important substances, *e.g.* vitamin D and related compounds [10,11].

The present summary provides a collection of information on the effects of major ionizing and non-ionizing irradiations on the function of cytochrome P450 and other drug metabolizing enzymes and transporters, considering also the effects on therapeutic treatment or human health.

TABULAR PRESENTATION

Data are presented in Tables 1 – 3 and formatted in columns 1 – 8: 1. **Species used for investigation**, 2. **Enzyme/Transporter**; 3. **Category**; 4. **Effectors**; 5. **Model; method used**; 6. **Effect** on particular enzyme or transporter; 7. **Remarks** about effects when stated by the cited authors to additionally characterize the effects. 8. **References**.

The data are sorted in Column 2 (**Enzymes/Transporters**), Column 4 (**Effectors**), and Column 1 (**Species**), for an easier approach to the information presented.

The tabulated data were obtained either *in vivo* (clinical experiments and whole animals) or *in vitro* using various models including clinical tissue samples, cell cultures, and microsomes following irradiation with the effectors.

It is important to emphasize that the experimental results can depend upon the model (human, animal) and/or method of irradiation used for investigation (doses, frequency, duration *etc.*), and contradictory or insufficient results might have been obtained. Results that might be of clinical importance are designated in the tables (bold-face font). Of the effectors presented in Table 1–3, a large number result from the environmental impacts (γ-, X-, and/or UV-radiation) and the reminder from clinical application (γ- and X-rays, or just ionizing radiation) on the expression/activity of both transporters and the enzymes. In most of the cases the results are interpreted as “increase” or “decrease” of expression of a particular enzyme/transporter, because this is of the lack of exact limits, diversity of ways of presenting results, and the large numbers of results obtained using immunohistochemistry or immunoblotting which are not always expressed quantitatively and thus making the results difficult to compare with those obtained by other methods [12]. However, standardized detection and quantification techniques and methods (*e.g.* quantitative real-time PCR (RT-PCR)) can provide more reliable comparisons of experimental results with therapy. In this respect it has been suggested that (of the techniques used to analyze drug transporters) flow cytometry may be preferred to immunoblots, mRNA blots, and immunocytochemical assays,

although other report shows immunoblots to be reasonably quantitative [13]. The use of functional flow cytometric tests (assessing modulator-induced changes in fluorophore retention and/or efflux) has been promoted because these allow evaluation of a protein activity, in contrast to immunochemical or molecular tests [14]. As discussed in the previous paper in this series [7], P-gp functional analysis should be preferred when testing effects of radiation in connection with specific clinical treatment (*e.g.*, cancers and other diseases) as a more sensitive predictor of chemoresistance than P-gp expression.

TRANSPORTERS

As presented in Table 1 (**Effects** and **Remarks** columns) the experimental results show that although in some cases inconsistent results and conclusions have been obtained for the same effectors using different methods and models, 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, 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 [15,16,17,18,19,20,21,22]. Interestingly, by using 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 [23]. 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 [20]. 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 [24,25], but no P-gp mRNA increases in human [24, 26] or in animal models [27,28,29,30,31,32]. This result supports the suggestion that standard X-ray radiation might affect clinical efficacy of subsequent or concurrent chemotherapy. When the parental drug-sensitive CEM cells were subjected to fractionated radiation, increased levels of MDR proteins and induced drug resistance was observed. However, fractionated radiation with X-rays resulted in decreased P-gp protein expression, and consequently the drug sensitivity of multidrug-resistant (MDR) cells was enhanced [33]. Using functional analysis, immunohistochemistry, and immunoblotting (following irradiation by either single doses of X-rays up to 25 Gy or fractionated radiation of rat blood-brain barrier), decreased P-gp protein expression and activity were observed [34,35], suggesting that in some cases radiation might be used to enhance the delivery of P-gp substrates to the brain. This result further shows that predictions of the irradiation effects are rather difficult and complex in nature. Chronic contamination of rats by depleted uranium (uranyl nitrate) in their drinking water (dose of 1 mg/rat/day for 9 months) resulted in an increase (34%) in ABCA1 transporter mRNA, which regulates cholesterol transport [36].

CYTOCHROME P450 ENZYMES

Summarized data on the effects of ionizing and non-ionizing radiation on cytochrome P450 enzymes are presented in Table 2. 7-Ethoxycoumarin O-deethylation (ECOD) activity was 7-fold and 2-fold higher in human placental microsomes samples (at term) from radioactivity-contaminated areas compared to a region considered to be “clean.” It was suggested that this effect could be related to the increased formation of reactive metabolites in placenta [54]. Experiments performed using animal models (chronic contamination of rats for 9 months by depleted uranium as uranyl nitrate in drinking water, dose of 1 mg/rat/day) showed that the cholesterol-oxidizing enzyme CYP46A1 displayed a 39% increase in mRNA level, as determined by RT-PCR [36]. In mice it was shown that differential effects of radiation on the components of the cytochrome P450 system were observed after whole body irradiation by γ-rays at different doses. The activities of cytochrome NADPH-P450 reductase, cytochrome b_5, and NADH-cytochrome reductase (as well as cytochrome P450 activity) were enhanced by irradiation doses up to ~5 Gy and decreased thereafter. The increase in cytochrome P450 activity was accompanied by the enhanced activity of glutathione transferase (Table 3), and administration of phenothiazines enhanced the radiation effect at lower irradiation doses on components of the cytochrome P450 system (except NADH-cytochrome b_5 reductase) by inducing cytochrome P450 enzymes, thus providing radioprotective action [55]. Also, whole body irradiation of mice with Ehrlich solid tumors with different doses of γ-rays (doses of 0–9 Gy, at a dose rate of 0.0153 Gy/s) caused increases in microsomal cytochrome P450 enzymes at doses up to 6 Gy and decreases thereafter [56]. In contrast, cytochrome P450 (Table 2) and glutathione transferase (Table 3) activities in the liver microsomal fractions of radiation-exposed rats were reduced in the latent and logarithmic phases of oncogenesis compared with non-irradiated rats having tumors. In this case, the radiation did not influence the enzyme activity of liver cytochrome P450 and glutathione transferase in the terminal stages of Guerin’s carcinoma growth [57].

The complexity of effects of radiation on cytochrome P450 activity are exemplified in the results obtained after short-term (3 and 30 day) and long-term (3–24 month) treatment of rats with neutron-activated UO_2 particles (9.3 kBq) [58]. After 3 days of treatment a decreased activity of 30% (testosterone 7α-hydroxylase) was observed, and after 30 days after treatment activity was enhanced by 70% (testosterone 7α-hydroxylase) and 40% (testosterone 15α-hydroxylase). After 1.5-year treatment, decreases in activity in lung testosterone 6β- (60%) and 6α-hydroxylase (30%) occurred; hepatic testosterone 16α-hydroxylase activity was decreased by 60–75% with both non-activated and neutron-activated particles [58].

A single subcutaneous administration of depleted uranium (as uranyl nitrate) to rats (at a sublethal toxic dose) affected bile acid cytochrome P450 activity in the following way: 7α-hydroxycholesterol plasma levels decreased by 52% at day 3, whereas microsomal CYP7A1 activity in the liver did not change significantly and mitochondrial CYP27A1 activity quintupled after day 1 [59]. Chronic exposure of rats with post-accidental doses of ^{137}Cs in drinking water for 3 months showed no significant change of CYP27A1 mRNA expression but increased the activity by 34% in rat liver [37,72,96]. However, experiments with rats

chronically exposed to depleted uranium in drinking water (1 mg/rat day) for 9 months showed that CYP3A1 mRNA expression was significantly higher in the brain (200%), liver (300%), and kidneys (900%) of exposed rats compared with control rats, and CYP3A2 mRNA levels were higher in the lungs (300%) and liver (200%), and CYP2B1 mRNA expression was elevated in the kidneys (300%). Expression of CYP1A1 mRNA did not change significantly during this study. It was suggested that the stimulating effect of uranium on cytochrome P450 enzymes might lead to hepatic or extrahepatic toxicity (or both) during drug treatment [60]. For further effects of ionizing irradiation on cytochrome P450 enzymes see Table 2.

The effects of UV irradiation were examined using human keratinocytes, and it was reported that combined UVA and UVB—UVA irradiation alone—caused induction of CYP4A11 mRNA expression and protein expression levels [8]. CYP1B1 mRNA and protein expression were induced by UVB irradiation of keratinocytes [51]. CYP1A1 was induced in keratinocytes, primary human blood lymphocytes, and a hepatoma cell line [61,62,63] slight induction of CYP19A1 (aromatase) mRNA was induced by combined UVA and UVB irradiation in keratinocytes [8]. Increased mRNA expression of toxicologically important CYP1A was observed in zebrafish larvae and embryos (exposed for varying time to UVA plus UVB, or UVB alone on two consecutive days), while embryos exposed to UVA alone had no effect on mRNA expression and UVB irradiation increased mRNA expression of CYP1B1 [9]. Induction of CYP1A1 and CYP1B1 mRNA and protein expression levels was suggested to be related to enhanced bioactivation of polycyclic aromatic hydrocarbons and other environmental pollutants in skin [61].

OXIDATIVE STRESS AND OTHER ENZYMES

Different effects (Table 3) on the oxidative stress enzymes (catalase (CAT), NADPH-quinone reductase (NOR), glyoxylase I (GLO1), superoxide dismutase (SOD)) were obtained after whole body irradiation of mice with Ehrlich solid tumor and non-tumor bearing animals with different doses of γ-radiation (0–9 Gy). While the activity of most of the enzymes increased with the radiation dose in the both tumor-bearing and non-tumor bearing mice up to 6 Gy and decreased thereafter (NADPH-quinone reductase, glyoxalase I, superoxide dismutase, xanthine oxidoreductase) [55,56,81], catalase was either not detected or decreased with the irradiation dose in both tumor and non-tumor animals [56,81]. At the same time a progressive increase was noticed in peroxidative damage with increasing irradiation dose [56]. As with the effects on cytochrome P450 enzymes (Table 2), administration of phenothiazines enhanced the effect of radiation at lower doses on the activities of superoxide dismutase and NADPH-quinone reductase but inhibited the activity of L-lactate dehydrogenase (LDH). The effect of phenothiazines was also connected to radioprotective action at lower irradiation doses in this case. In addition, phenothiazines inhibited lipid peroxidation and xanthine oxidoreductase (XOR) [55]. Taking superoxide dismutase as an example, the effects of the ionizing irradiation were the following: the lower doses of γ-irradiation or ionizing radiation (up to 6 Gy) enhanced the enzyme activity, but decreases of activity and protein levels were observed at higher doses. This result was confirmed using different models and methods, including human models [55,82,83]. It was reported that the decrease of the activity and protein levels at higher radiation doses could be

reversed by supplementation with extracts of *Xylopia aethiopica* and vitamin C [82]. At lower occupational doses (*e.g.*, exposed medical workers), enhanced activity of superoxide dismutase might provide protection against the increased production of reactive oxygen species but that dysfunction of enzyme system can occur following higher doses of irradiation [84]. Similarly, chronic UV irradiation also caused increased superoxide dismutase activity and mRNA expression in both human and in animal models [9,85] but decreased activity was observed after single UVB radiation of mice skin [86].

CONCLUSION

As reported before [7], increases in expression levels of cytochrome P450 enzymes (for instance CYP1B1 and CYP2J2) and transporters (MRP1) in tumor cells and tissues have been suggested as tumor markers in the diagnosis and prognosis of malignancies and/or other diseases. However, results reported before [1,2] and in this summary show that when using such markers and before complex considerations one has to take into account the effects of drug and diseases, as well as natural (UV) or “artificial” radiation coming from the environment (e. g., nuclear plant disasters, radon exposure) or applied clinically (γ- and X-rays). This summary presents 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 ADME properties of drugs.

Acknowledgments

This work is dedicated to the family of the corresponding author (R.S.), including his wife Vjekoslava, son Borut, and daughter Petra.

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Table 1

Effects of Ionizing and Non-ionizing Irradiation on Expression and Activity of Transporters

Species	Transporter	Category	Effectors	Model; method used	Effects	Remarks	Reference
Rat	**ABCA1, ABC1**	Environmental impact	Cesium contamination	chronic exposure with post-accidental doses of ^{137}Cs in drinking water for 3 months, at a dose of 6500 Bq/l (150 Bq/rat/day), liver, microsomes; quantitative RT-PCR	no change of mRNA expression		[37]
Mice	**ABCA1, ABC1**	Environmental impact	Uranium contamination	chronic exposure for 8 months by depleted uranium through drinking water 20 mg/L, cerebral cortex; RT-PCR	increase of mRNA level expression by 52%		[38]
Rat	**ABCA1, ABC1**	Environmental impact	Uranium contamination	chronic contamination for 9 months by depleted uranium (uranyl nitrate) through drinking water of dose 1 mg/rat/day, brain; RT-PCR	increase of mRNA level expression by 34%	dose corresponds to twice the highest concentration found naturally in Finland	[36]
Rat	**ABCA1, ABC1**	Environmental impact	Uranium contamination	low-level chronic ingestion of depleted uranium in drinking water for 9 months, 40mg/kg, liver; RT-PCR	increase of mRNA expression (to 154%) and protein expression (125% but not significant)		[39]
Human	**ABCA1, ABC1**	Clinical impact	X-rays	malignant glioma U87-MG cells, 200KV x-ray-irradiation; immunoblotting	increase of protein expression	temozolomide co-treatment enhanced expression rate, suggested to be involved in drug resistance following radiation treatment	[40,18]
Rat	**ABCG5**	Environmental impact	Cesium contamination	chronic exposure with post-accidental doses of ^{137}Cs in drinking water for 3 months, at a dose of 6500 Bq/l (150 Bq/rat/day), liver; quantitative RT-PCR	decrease of mRNA expression (by 42%)		[37]
Rat	**ABCG5**	Environmental impact	Uranium contamination	low-level chronic ingestion of depleted uranium in drinking	increase of hepatic gene expression		[39]

Species	Transporter	Category	Effectors	Model; method used	Effects	Remarks	Reference
				water for 9 months, 40 mg/kg, liver; RT-PCR water for 9 months, 40 mg/kg, liver; RT-PCR			
Rat	**ABCG8**	Environmental impact	Uranium contamination	low-level chronic ingestion of depleted uranium in drinking water for 9 months, 40 mg/kg, liver; RT-PCR	increase of hepatic gene expression		[39]
Human	**EAAT1, GLAST, SLC1A3**	Clinical impact	γ-radiation, γ-rays	NTera2-derived neurons as pure cultures exposed to doses of 10 cGy, 50 cGy and 2 Gy gamma rays, analyzed at 3 h, 2 days and 7 days after exposure; immunocytochemical labeling, laser scanning cytometry, immunoblotting, glutamate uptake	linear increase of protein expression and appeared to double between times, increase of glutamate uptake	no significant differences between doses of radiation	[41]
Human	**EAAT1, GLAST, SLC1A3**	Clinical impact	γ-radiation, γ-rays	NTera2-derived astrocytes as pure cultures exposed to doses of 10 cGy, 50 cGy and 2 Gy γ-rays, analyzed at 3 h, 2 days and 7 days after exposure; immunocytochemical labeling, laser scanning cytometer, immunoblotting, glutamate uptake	increase of protein expression approximately 1.5-fold between 3h and 2 days and about fivefold between day 2 and day 7 after irradiation, significant decrease in glutamate uptake 2 days after irradiation with all three doses and returned to baseline levels	no significant differences between doses of radiation	[41]
Human	**EAAT2, GLT-1, SLC1A2**	Clinical impact	γ-radiation, γ-rays	NTera2-derived neurons as pure cultures exposed to doses of 10 cGy, 50 cGy and 2 Gy γ-rays, analyzed at 3 h, 2 days and 7 days after exposure; immunocytochemical labeling, laser scanning cytometry, immunoblotting, glutamate uptake	dose-dependent increase in protein expression was seen between doses of 10 and 50 cGy, increase of glutamate uptake	no significant differences between doses of radiation	[41]
Human	**EAAT2, GLT-1, SLC1A2**	Clinical impact	γ-radiation, γ-rays	NTera2-derived astrocytes as pure cultures exposed to doses of 10 cGy, 50 cGy and 2 Gy γ-rays,	increase of protein expression approximately 1.5-fold between 3h and 2 days and about fivefold between day 2 and day 7	no significant differences between doses of radiation	[41]

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Species	Transporter	Category	Effectors	Model; method used	Effects	Remarks	Reference
				analyzed at 3 h, 2 days and 7 days after exposure; immunocytochemical labeling, laser scanning cytometry, immun	7 days after irradiation, significant decrease in glutamate uptake 2 days after irradiation with all three doses and returned to baseline levels		
Human	**EAAT3, EAAC1, SLC1A1**	Clinical impact	γ-radiation, γ-rays	NTera2-derived neurons as pure cultures exposed to doses of 10 cGy, 50 cGy and 2 Gy γ-rays	significant increase of protein expression was observed in EAAT3 after 50 cGy 7 days after exposure, increase of glutamate uptake	no significant differences between doses of radiation	[41]
Human	**EAAT3, EAAC1, SLC1A1**	Clinical impact	γ-radiation, γ-rays	NTera2-derived astrocytes as pure cultures exposed to doses of 10 cGy, 50 cGy and 2 Gy γ-rays, analyzed at 3 h, 2 days and 7 days after exposure; immunocytochemical labeling, laser scanning cytometry, immunoblotting, glutamate uptake	increase of expression over time, 16-fold 7 days after 50 cGy irradiation, low level expression, significant decrease in glutamate uptake 2 days after irradiation with all three doses and returned to baseline levels	no significant differences between doses of radiation	[41]
Human	**EAAT4, SLC1A6**	Clinical impact	γ- radiation, γ-rays	NTera2-derived neurons as pure cultures exposed to doses of 10 cGy, 50 cGy and 2 Gy γ-rays, analyzed at 3 h, 2 days and 7 days after exposure; immunocytochemical labeling, laser scanning cytometry, immunoblotting, glutamate uptake	increase of protein expression 3 h after irradiation, increase of glutamate uptake	no significant differences between doses of radiation	[41]
Human	**EAAT4, SLC1A6**	Clinical impact	γ-radiation, γ-rays	NTera2-derived astrocytes as pure cultures exposed to doses of 10 cGy, 50 cGy and 2 Gy γ-rays, analyzed at 3 h, 2 days and 7 days after exposure; immunocytochemical labeling, laser scanning cytometry, immunoblotting, glutamate uptake	two-fold increase of protein expression between 3 h and day after irradiation, low level expression, significant decrease in glutamate uptake 2 days after irradiation with all three doses and returned to baseline levels	no significant differences between doses of radiation	[41]

Species	Transporter	Category	Effectors	Model; method used	Effects	Remarks	Reference
Human	**LRP (lung resistance-related protein)**	Clinical impact	Ionizing irradiation	fractionated irradiation, breast cancer cell lines irradiated with a total dose of 27 Gy, five fractions of 1.8 Gy per week; RT-PCR, flow cytometry	increase of mRNA expression and protein level expression in irradiated cells		[20]
Human	**LRP (lung resistance-related protein)**	Clinical impact	Ionizing irradiation	fractionated irradiation, colon cancer cell lines irradiated with a total dose of 27 Gy, five fractions of 1.8 Gy per week; RT-PCR, flow cytometry	no increase of mRNA expression, high increase of protein level in irradiated cells	significant resistance to cisplatin, doxorubicin and bendamustine	[20]
Human	**LRP (lung resistance-related protein)**	Clinical impact	X-rays	fractionated irradiation, SW620 colon carcinoma cells exposed to either 27 Gy in 1.8-Gy daily fractions; semiquantitative RT-PCR, flow cytometry	gene activated only shortly after radiation	irradiated cells less sensitive to cisplatin but not to doxorubicin	[22]
Human	**MDR1, P-glycoprotein, P-gp, ABCB1**	Clinical impact	γ-radiation, γ-rays	cervical carcinoma HeLa cells exposed to 10 daily fractions of 0.17 Gy γ-rays; immunochemistry	increase of protein expression	increased resistance to vincristine and vinblastine	[15]
Human	**MDR1, P-glycoprotein, P-gp, ABCB1**	Clinical impact	γ-radiation, γ-rays	hepatocellular carcinoma HepG2 cells (G cells) were gamma-radiation treated of 2 Gy for 10 days (G2) or 10 Gy for 2 days (G10) and then doxorubicin (Dox) treated as continuous exposure for up to 10 microM; Dox accumulation assay, immunohistochemistry, immunoblotting, Southern blotting, RT-PCR	increase of protein and mRNA expression in irradiated cells before Dox treatment	radiation treatment may lead to a development of highly resistant phenotype	[21]
Human	**MDR1, P-glycoprotein, P-gp, ABCB1**	Clinical impact	γ-radiation, γ-rays	fractionated irradiation, MDR KB-VI cancer cells exposed to 1400 and 2800 cGy ionizing radiation administered in 7 and 14 fractions (at 200 cGy per	decrease in MDR1 extrachromosomal gene copy, decrease of protein level	low to moderate doses of ionizing radiation reduce multidrug resistance with improved therapeutic response (vinblastine,	[43]

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Species	Transporter	Category	Effectors	Model; method used	Effects	Remarks	Reference
				fraction/day, with fractionday, with ^{137}Cs, cells40 Exactor); immunoblotting, FISH analysis		doxorubicin, colchicine, cisplatin) for some cancers due to loss of extrachromosomally amplified genes from tumor cells	
Human	**MDR1, P-glycoprotein, P-gp, ABCB1**	Clinical impact	γ-radiation, γ-rays	fractionated irradiation, esophageal cancer biopsy samples; quantitative RT-PCR, immunoblotting	increased initial mRNA expression decreased after 7 irradiation Gy/f, 14 fractions	differentially modulated MDR1 expression by different doses of fractionated radiation	[44]
Human	**MDR1, P-glycoprotein, P-gp, ABCB1**	Clinical impact	Ionizing irradiation	tumor cell lines (MCF-7, LXF and Sk-Mel), single doses (5, 10 and 20 Gy);	no significant change of mRNA expression		[42]
Human	**MDR1, P-glycoprotein, P-gp, ABCB1**	Clinical impact	Ionizing irradiation	radiotherapy, stage I primary breast cancer specimens; immunohistochemistry	increase of protein expression		[46]
Human	**MDR1, P-glycoprotein, P-gp, ABCB1**	Clinical impact	Ionizing irradiation	irradiated nasopharyngeal carcinoma (NPC) CNE1 cells; immunoblotting, RT-PCR, flow cytometry	long-term overexpression, reduction in intracellular daunorubicin accumulation	irradiation decreased the chemotherapy sensitivity of CNE1 cells	[17]
Human	**MDR1, P-glycoprotein, P-gp, ABCB1**	Clinical impact	Ionizing irradiation	fractionated irradiation, breast cancer cell lines irradiated with a total dose of 27 Gy, five fractions of 1.8 Gy per week; quantitative RT-PCR, flow cytometry	increase of mRNA expression, low increase of protein level		[20]
Human	**MDR1, P-glycoprotein, P-gp, ABCB1**	Clinical impact	Ionizing irradiation	fractionated irradiation, colon cancer cell lines irradiated with a total dose of 27 Gy, five fractions of 1.8 Gy per week; quantitative RT-PCR, flow cytometry	no increase of mRNA expression, high increase of protein level in irradiated cells,	significant resistance to cisplatin, doxorubicin and bendamustine	[20]
Murine	**MDR1, P-glycoprotein, P-gp, ABCB1**	Clinical impact	Ionizing irradiation	NIH 3T3 cells treated with single doses of 5, 10 and 20 Gy	no change of mRNA expression		[45]
Human	**MDR1, P-glycoprotein, P-gp, ABCB1**	Environmental impact	UV irradiation	KB carcinoma cells irradiated with UV light (16 J/m2, 254	induction of gene expression, transcriptional	induction of gene expression through a common stress-	[49,50,51]

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Species	Transporter	Category	Effectors	Model; method used	Effects	Remarks	Reference
				nm); luciferase activity, Northern analysis, immunoblotting nm); luciferase activity, Northern analysis, immunoblotting nm); luciferase activity, Northern analysis, immunoblotting nm); luciferase activity, Northern analysis, immunoblotting	activation of the MDR1 gene promoter	induced signal transduction suggested	
Chinese hamster	**MDR1, P-glycoprotein, P-gp, ABCB1**	Clinical impact	X-rays	fractionated irradiation, Chinese hamster ovary cell lines (ten fractions of 9 Gy), exposure to multiple lethal doses, or to a single 30-Gy dose of radiation; immunoblotting, mRNA blotting	increase of protein level, no gene amplification, no significant alteration in expression and mRNA levels	drug cross-resistance to vinca alkaloids (vincristine), epipodophyllotoxins (etoposide), gramicidin D, taxol, puromycin, and navelbine, but sensitive to anthracyclines (daunomycin or mitoxantrone) regulated by post-translational stability	[27,28,29,30,31,32]
Human	**MDR1, P-glycoprotein, P-gp, ABCB1**	Clinical impact	X-rays	fractionated irradiation, lymphoblastic leukemia CEM/MDR cell sublines; susceptibility to anticancer drugs	decrease of protein expression	drug sensitivity of multidrug-resistant (MDR) cells could be enhanced by fractionated irradiation	[33]
Human	**MDR1, P-glycoprotein, P-gp, ABCB1**	Clinical impact	X-rays	fractionated irradiation, small-cell lung cancer H69 SCLC cells, X-rays to an accumulated dose of 37.5 Gy over 8 months; immunoblotting	no change in protein expression		[25]
Human	**MDR1, P-glycoprotein, P-gp, ABCB1**	Clinical impact	X-rays	squamous carcinoma oral cavity T167 cell lines, exposed to either a standard clinical dose of 2 GY and 7GY or low-dose fractionated irradiation therapy (LDFRT) delivered as 0.5 Gy in four fractions; RT-PCR, immunoblotting, activity as efflux of rhodamine 123	increase of expression and activity in response to conventional 2-Gy and high-dose 7-Gy radiation, no increase during LDFRT.	the up-regulation of the transport activity may lead to radio-and chemoresistance during the conventional and high-dose ionizing radiation treatments, but not during LDFRT	[19]
Human	**MDR1, P-glycoprotein, P-gp, ABCB1**	Clinical impact	X-rays	radiotherapy, primary oral squamous carcinoma tissues; immunohistochemistry	increase of expression in tumor tissue	standard radiation might affect the efficacy of subsequent or	[52]

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Species	Transporter	Category	Effectors	Model; method used	Effects	Remarks	Reference
						concurrent chemotherapy concurrent chemotherapy	
Human	**MDR1, P-glycoprotein, P-gp, ABCB1**	Clinical impact	X-rays	fractionated irradiation, human epidermoid lung carcinoma xenograft HXL55 exposed to seven irradiation treatments of 10 Gy over period of 9 months; immunofluorescence, Southern blotting	increase of protein expression, no gene amplification	increased resistance to vincristine	[26]
Human	**MDR1, P-glycoprotein, P-gp, ABCB1**	Clinical impact	X-rays	fractionated irradiation, human ovarian tumor cells exposed to 10 fractions of 5 Gy (the total radiation dose administered was50 Gy); immuno and mRNA blotting or RNase protection assays	increase of protein expression, no increase of mRNA expression	increased resistance to vincristine and etoposide	[24]
Human	**MDR1, P-glycoprotein, P-gp, ABCB1**	Clinical impact	X-rays	fractionated irradiation, human ovarian tumor cells SK-OV-3 exposed to 2 Gy twice-daily fractions for 5 days on two consecutive weeks; immunocytochemistry	increase of protein expression		[53]
Human	**MDR1, P-glycoprotein, P-gp, ABCB1**	Clinical impact	X-rays	fractionated irradiation, parental drug-sensitive lymphoblastic leukemia CEM cells; susceptibility to anticancer drugs	increase of protein expression	induced drug resistance in the parental drug-sensitive CEM cells	[33]
Rat	**MDR1, P-glycoprotein, P-gp, ABCB1**	Clinical impact	X-rays	right brain hemispheres irradiated with single doses of 2–25 Gy, or with fractionated irradiation (4×5 Gy), followed by cyclosporine A (CsA) 5 days later, brain samples; immunohistochemistry, immunoblotting, [^{11}C]carvedilol uptake using quantitative autoradiography	decrease of protein expression and activity 10 days after start of irradiation, and between day 15 and 20 after single dose irradiation, and increased again thereafter	suggested that that brain irradiation could be used to enhance the delivery of P-gp substrates to the brain.	[34,35]

Species	Transporter	Category	Effectors	Model; method used	Effects	Remarks	Reference
Murine	**MDR1 A, P-glycoprotein, P-gp, ABCB1A**	Clinical impact	Ionizing irradiation	fractionated irradiation, Ehrlich ascites tumor cells (EHR2), 60 Gy; immunoblotting, semiquantitative RT-PCR	increase of protein expression (threefold), mRNA not detectable	increased resistance to etoposide and vincristine	[23]
Murine	**MDR1B, P-glycoprotein, P-gp, ABCB1B**	Clinical impact	Ionizing irradiation	fractionated irradiation, Ehrlich ascites tumor cells (EHR2), 60 Gy; immunoblotting, semiquantitative RT-PCR	increase of protein expression (threefold), slight reduction of mRNA expression	increased resistance to etoposide and vincristine	[23]
Rat	**MRP**	Clinical impact	γ-radiation, Gamma-rays	isolated hepatocytes in vitro, dose 8 Gy; real-time PCR, immunoblotting	increase of mRNA expression and protein level		[47]
Rat	**MRP**	Clinical impact	γ-radiation, γ-rays	liver were irradiated in vivo with 6 MV photons (dose rate 2.4 Gy/min); real-time PCR, immunoblotting	increase of mRNA expression and protein level		[47]
Human	**MRP1, MRP, GS-X, ABCC1**	Clinical impact	γ-radiation, γ-rays	fractionated irradiation, CCRF-CEM (CEM) human T-cell leukemia cell line, total 75 Gy (10 cycles of 1.5 Gy daily for 5 days).	6-fold increase in protein level, increase of mRNA expression	mRNA increased within 4 hr which, by 24 hr, was greater than 5-fold and suggested to be involved in drug resistance following radiation treatment, buthionine sulphoximine reversed the daunorubicin resistance	[16,18]
Human	**MRP1, MRP, GS-X, ABCC1**	Clinical impact	Ionizing irradiation	tumor cell lines (MCF-7, LXF and Sk-Mel), single doses (5, 10 and 20 Gy);	no significant change of mRNA expression		[42]
Human	**MRP1, MRP, GS-X, ABCC1**	Clinical impact	Ionizing irradiation	fractionated irradiation, breast cancer cell lines irradiated with a total dose of 27 Gy, five fractions of 1.8 Gy per week; quantitative RT-PCR, flow cytometry	increase of mRNA expression and protein level in irradiated cells		[20]
Human	**MRP1, MRP, GS-X, ABCC1**	Clinical impact	Ionizing irradiation	fractionated irradiation, colon cancer cell lines irradiated with a total dose of 27 Gy, five	no increase of mRNA expression, high increase of protein level in irradiated cells	significant resistance to cisplatin,	[20]

Species	Transporter	Category	Effectors	Model; method used	Effects	Remarks	Reference
				fractions of 1.8 Gy per week; quantitative RT-PCR, flow cytometry		doxorubicin and	
				fractions of 1.8 Gy per week; quantitative RT-PCR, flow cytometry		lomustine	
				fractions of 1.8 Gy per week; quantitative RT-PCR, flow cytometry			
Murine	**Mrp1, Mrp, GS-X, Abcc1**	Clinical impact	Ionizing irradiation	fractionated irradiation, Ehrlich ascites tumor cells (EHR2), 60 Gy; immunoblotting, semiquantitative RT-PCR	increase of protein expression (8-fold), increase of mRNA expression (6-fold)	increased resistance to etoposide and vincristine	[23]
Human	**MRP1, MRP, GS-X, ABCC1**	Clinical impact	X-rays	fractionated irradiation, small-cell lung cancer H69 SCLC cells treated to an accumulated dose of 37.5 Gy over 8 months; immunoblotting	increase of protein expression	may account for the cisplatin resistance	[25]
Human	**MRP1, MRP, GS-X, ABCC1**	Clinical impact	X-rays	fractionated irradiation, human ovarian tumor cells SK-OV-3 exposed to 2 Gy twice-daily fractions for 5 days on two consecutive weeks; immunocytochemistry	increase of expression		[54]
Human	**MRP2, cMOAT, ABCC2**	Clinical impact	X-rays	fractionated irradiation, small-cell lung cancer H69 SCLC cells treated to an accumulated dose of 37.5 Gy over 8 months; immunoblotting	increase of protein expression	may account for the cisplatin resistance	[25]
Human	**MRP2, cMOAT, ABCC2**	Clinical impact	X-rays	fractionated irradiation, SW620 colon carcinoma cells exposed to either 27 Gy in 1.8-Gy daily fractions; semiquantitative RT-PCR, flow cytometry	increase of gene expression up to 3 weeks after radiation	irradiated cells less sensitive to cisplatin but not to doxorubicin	[22]
Mice	**SGLT1, SLC5A1**	Environ mental impact	γ-radiation, γ-rays	proximal jejunum sections; whole body irradiation with ^{137}Cs γ-rays at doses of 0, 7, 8.5, or 10 Gy, real-time PCR	decreased mRNA abundance	d-glucose uptake decreased by approximately 10–20% by day 8 post irradiation; vitamin A supplementation had no effect on clinical or transport parameters	[48]

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Species	Transporter	Category	Effectors	Model; method used	Effects	Remarks	Reference
Mice	**VAChT (vesicular acetylcholine transporter)**	Environmental impact	Uranium contamination	chronic exposure for 8 months by depleted uranium through drinking water 20 mg/L, cerebral cortex; RT-PCR	increase of mRNA level expression by 120%		[38]

Table 2

Effects of Ionizing and Non-ionizing Irradiation on Expression and Activity of Cytochrome P450 Enzymes

Species	Enzyme	Category	Effectors	Model; method used	Effects	Remarks	References
Mice	**CPR (cytochrome P450 reductase)**	Environmental impact	γ-radiation, γ-rays	whole body irradiation, different doses of gamma-rays at 1.38 Gy/min, liver; activity	activity increased up to 5 Gy (to 125%) and decreased thereafter (to 105% after 9 Gy)	administration of phenothiazines enhanced the radiation effect at lower doses **providing the radioprotective action**	[55]
Mice	**CYB5 (cytochrome b_5)**	Environmental impact	γ-radiation, γ-rays	whole body irradiation, different doses of gamma-rays at 1.38 Gy/min, liver; activity	holoprotein increased up to 5 Gy (to 120%) and decreased thereafter (to 83% with 9 Gy)	administration of phenothiazines enhanced the radiation effect at lower doses **providing radioprotective action**	[55]
Mice	**CYB5R (cytochrome b_5 reductase)**	Environmental impact	γ-radiation, γ-rays	whole body irradiation, different doses of γ-rays at 1.38 Gy/min, liver; activity	activity enhanced up to 3 Gy (to 125%)and decreased thereafter (to 104% after 9 Gy)	administration of phenothiazines did not affect radiation effect	[55]
Mice	**CYP**	Clinical impact	γ-radiation, γ-rays	whole body irradiation of mice with Ehrlich solid tumors with different doses of gamma rays (0–9 Gy) at a dose rate of 0.0153 Gy/s, solid tumor, microsomal fractions; content measured as CO difference spectrum	increase of content with dose up to 6 Gy and decreased thereafter		[56]
Mice	**CYP**	Environmental impact	γ-radiation, γ-rays	whole body irradiation, different doses of gamma-rays at 1.38 Gy/min, liver; activity	holoprotein enhanced up to 5 Gy (to 119%) and decreased thereafter (to 108% after 9 Gy)	administration of phenothiazines enhanced the radiation effect at lower doses **providing the radioprotective action**	[55]
Human	**CYP**	Clinical impact	Ionizing irradiation	fractionated irradiation, ADF human astrocytoma cell line treated with 5 Gy for 4 consecutive days;	upregulation of gene expression	suggested role in the **reactive oxygen species (ROS) formation**	[64]

Species	Enzyme	Category	Effectors	Model; method used	Effects	Remarks	References
				immunoblotting, microarray analysis immunoblotting, microarray analysis			
Rat	**CYP**	Clinical impact	Ionizing irradiation	preliminary radiation-exposed, transplanted Guerin's carcinoma, liver, microsomes; activity	decreased activity in the latent and logarithmic phases of oncogenesis, no effect on terminal stages of Guerin's carcinoma growth		[57]
Human	**CYP**	Environmental impact	Radioactivity-contaminated areas	placental samples at term, microsomes; 7-ethoxycoumarin O-deethylase (ECOD)	enhanced ECOD activity	ECOD activity was 7-fold and 2-fold higher compared to the region considered to be "clean"; **increased formation of reactive metabolites** suggested	[54]
Rat	**CYP**	Environmental impact	Uranium contamination	short-term (3 and 30 days) and long-term (3–24 months) treatment with neutron-activated UO_2 particles (9.3 kBq), liver microsomes; testosterone 7α- and 15α-hydroxylase activity	decreased activity by 30% (7α-) at 3 days treatment, at 30 days after treatment activity enhanced by 70% (7α-) and 40% (15α-)		[58]
Rat	**CYP**	Environmental impact	Uranium contamination	long-term (3–24 months) treatment with neutron-activated UO_2 particles (9.3 kBq, cumulated lung dose 0.4–0.66 Gy, 131 and 182 kBq), lung, liver; testosterone 7β-, 6α-, and 16α-hydroxylase activity	at the 1.5-year treatment decreases in lung testosterone 6β-hydroxylase (60%) and testosterone 6α-hydroxylase (30%) activities, hepatic testosterone 16α-hydroxylase activity decreased by 60–75% with both non-activated and neutron-activated particles		[58]
Human	**CYP**	Environmental impact	UV irradiation	cultures of fibrobroblasts in a collagen matrix as the dermal component and keratinocytes as the epidermal component, UVB irradiation; calcitriol formation from 7-dehydrocholesterol, HPLC, GC-MS	wavelength- and dose dependent ultraviolet-B-triggered conversion of 7-dehydrocholesterol to calcitriol observed		[10,11]

Species	Enzyme	Category	Effectors	Model; method used	Effects	Remarks	References
Rat	**CYP**	Clinical impact	X-rays	preliminary radiation-exposed rats with Guerin's carcinoma, liver, microsomal fraction; activity	activity reduced		[57]
Human	**CYP19A1 (Aromatase)**	Environmental impact	UV irradiation	keratinocytes, combined UVA and UVB irradiation, microsomes; gel electrophoresis, RT-PCR	slight induction of mRNA expression		[8]
Zebrafish	**CYP1A**	Environmental impact	UV irradiation	embryos exposed for varying time of UVA plus UVB, or UVB alone on two consecutive days; spectophotometry, RT-PCR	increase of mRNA expression		[9]
Zebrafish	**CYP1A**	Environmental impact	UV irradiation	embryos exposed for varying time of UVA on two consecutive days; spectophotometry, RT-PCR	no effect on mRNA expression		[9]
Zebrafish	**CYP1A**	Environmental impact	UV irradiation	larvae exposed to single 8-h long UVB exposure; spectophotometry, RT-PCR	increase of mRNA expression		[9]
Rat	**CYP1A1**	Environmental impact	Uranium contamination	chronically exposed to depleted uranium (as uranyl nitrate) in drinking water, 1 mg/(rat day) for 9 months, brain, liver, lung, kidney, intestine; RT-PCR	no change in expression of mRNA		[60]
Human	**CYP1A1**	Environmental impact	UV irradiation	keratinocytes, UVB irradiation; immunohistochemistry, semiquantitative RT-PCR, immunoblotting	induction of mRNA and protein		[61]
Human	**CYP1A1**	Environmental impact	UV irradiation	hepatoma cell line HepG2, UVB irradiation; immunohistochemistry, RT-PCR, immunoblotting, 6-formylindolo[3,2-	initial repression (3 hours after treatment) and induction of mRNA following prolonged treatment (9 hours after treatment), inhibition of activity		[63]

Species	Enzyme	Category	Effectors	Model; method used	Effects	Remarks	References
				b]carbazole metabolism]carbazole metabolism			
Human	**CYP1A1**	Environmental impact	UV irradiation	keratinocytes, UVB irradiation; RT-PCR	induction of mRNA and protein	induction was higher in the presence of tryptophan	[62]
Human	**CYP1A1**	Environmental impact	UV irradiation	primary human blood lymphocytes, UVB irradiation; immunohistochemistry, RT-PCR, immunoblotting	induction of mRNA and protein	induction was higher in the presence of tryptophan	[62]
Mice	**CYP1A1**	Environmental impact	UV irradiation	Hepa-1 cells, UVB irradiation; immunohistochemistry, RT-PCR, immunoblotting	induction of mRNA and protein		[62]
Rat	**CYP1A1**	Environmental impact	UV irradiation	liver, UVB irradiation; EROD activity	induction of activity		[65]
Rat	**CYP1A2**	Environmental impact	Gamma radiation, Gamma-rays	whole body irradiation of 3 gray (G) at a dosage rate of 12.5 cG/min from a ^{60}Co radiation source, liver, microsomes; immunoblotting, mRNA blotting	no change in the mRNA expression at 24 h		[66]
Rat	**CYP1A2**	Environmental impact	Uranium contamination	uranyl nitrate solution injected once via the tail vein (5 mg/kg), plasma, liver, microsomes; chlorzoxazone pharmacokinetics i.v., microsomal metabolism, immunoblotting, mRNA blotting	no change of protein or mRNA expression	induced acute renal failure observed	[67,68,69,70,71]
Human	**CYP1B1**	Environmental impact	UV irradiation	keratinocytes, UVB irradiation; immunohistochemistry, semiquantitative RT-PCR, immunoblotting	induction of mRNA and protein	connected with enhanced bioactivation of polycyclic aromatic hydrocarbons and other environmental pollutants	[61]
Zebrafish	**CYP1B1**	Environmental impact	UV irradiation	embryos exposed for varying time of UVB on two consecutive	increase of mRNA expression		[9]

Species	Enzyme	Category	Effectors	Model; method used	Effects	Remarks	References
				days; spectophotometry, RT-PCR days; spectophotometry, RT-PCR days; spectophotometry, RT-PCR			
Zebrafish	**CYP1B1**	Environmental impact	UV irradiation	larvae exposed to single 8-h long UVB exposure; spectophotometry, RT-PCR	increase of mRNA expression		[9]
Zebrafish	**CYP1C1**	Environmental impact	UV irradiation	larvae exposed to single 8-h long UVB exposure; spectophotometry, RT-PCR	no effect on mRNA expression		[9]
Zebrafish	**CYP1C2**	Environmental impact	UV irradiation	larvae exposed to single 8-h long UVB exposure; spectophotometry, RT-PCR	no effect on mRNA expression		[9]
Zebrafish	**CYP1D1**	Environmental impact	UV irradiation	larvae exposed to single 8-h long UVB exposure; spectophotometry, RT-PCR	no effect on mRNA expression		[9]
Rat	**CYP24A1**	Environmental impact	Cesium contamination	chronic exposure with post-accidental doses of ^{137}Cs in drinking water for 3 months, at a dose of 6500 Bq/l (150 Bq/rat/day), kidney; RT-PCR, activity ([4-^{14}C]cholesterol as substrate)	no significant change of mRNA expression		[72]
Rat	**CYP24A1**	Environmental impact	Uranium contamination	single acute depleted uranium (as uranyl nitrate) intragastric administration (204 mg/kg body weight dissolved in 1.5 ml), kidney; RT-PCR	no change in expression of mRNA	contamination by short-term exposure to depleted uranium	[73]
Rat	**CYP24A1**	Environmental impact	Uranium contamination	chronic contamination for 9 months by depleted uranium (uranyl nitrate) through drinking water of dose 1 mg/rat/day, brain, mitochondria; RT-PCR	mRNA not detected	dose corresponds to the double of highest concentration found naturally in Finland	[74]

Species	Enzyme	Category	Effectors	Model; method used	Effects	Remarks	References
Rat	**CYP24A1**	Environmental impact	Uranium contamination	chronic contamination for 9 months by depleted uranium (uranyl nitrate) through drinking water of dose 1 mg/rat/day, kidney, mitochondria; RT-PCR	decreased mRNA expression by 38%,	dose corresponds to the double of highest concentration found naturally in Finland	[74]
Rat	**CYP24R1**	Environmental impact	Uranium contamination	chronic contamination for 9 months by depleted uranium (uranyl nitrate) through drinking water of dose 1 mg/rat/day, liver, mitochondria; RT-PCR	no change of mRNA level expression	dose corresponds to the double of highest concentration found naturally in Finland	[74]
Rat	**CYP27A1**	Environmental impact	Cesium contamination	chronic exposure with post-accidental doses of 137Cs in drinking water for 3 months, at a dose of 6500 Bq/l (150 Bq/rat/day), liver, mitochondria; quantitative RT-PCR, [4-^{14}C]Cholesterol 27-hydroxyation activity	no significant change of mRNA expression, increase of activity by 34%		[37,72,96]
Rat	**CYP27A1**	Environmental impact	Cesium contamination	chronic exposure with post-accidental doses of 137Cs in drinking water for 3 months, at a dose of 6500 Bq/l (150 Bq/rat/day), brain; RT-PCR	no significant change of mRNA expression		[72]
Rat	**CYP27A1**	Environmental impact	Uranium contamination	single acute depleted uranium (as uranyl nitrate) intragastric administration (204 mg/kg body weight dissolved in 1.5 ml), liver, mitochondria; RT-PCR, [4-^{14}C]Cholesterol 27-hydroxyation activity	no gross modifications in the expression, activity decreased at day 1 days and increased (threefold) at day 3 after treatment		[73]
Rat	**CYP27A1**	Environmental impact	Uranium contamination	single depleted uranium (as uranyl nitrate) subcutaneous administration, sublethal toxic dose of 11.5 mg/kg, liver, mitochondria; [4-^{14}C]cholesterol 27-hydroxylation activity	activity quintupled at day 1 after treatment and then returned to levels similar to controls at day 3		[59]

Species	Enzyme	Category	Effectors	Model; method used	Effects	Remarks	References
Rat	**CYP27A1**	Environmental impact	Uranium contamination	chronic contamination for 9 months by depleted uranium (uranyl nitrate) through drinking water of dose 1 mg/rat/day, brain, mitochondria; RT-PCR	decreased mRNA level expression by 32%, activity decreased at day 1 days and increased (threefold) at day 3 after treatment	dose corresponds to the double of highest concentration found naturally in Finland	[74]
Rat	**CYP27A1**	Environmental impact	Uranium contamination	chronic contamination for 9 months by depleted uranium (uranyl nitrate) through drinking water of dose 1 mg/rat/day, liver, mitochondria; RT-PCR, [4-^{14}C] cholesterol 27-hydroxyastion activity	no change of mRNA level expression or activity	dose corresponds to the double of highest concentration found naturally in Finland	[74]
Rat	**CYP27B1**	Environmental impact	Cesium contamination	chronic exposure with post-accidental doses of ^{137}Cs in drinking water for 3 months, at a dose of 6500 Bq/l (150 Bq/rat/day), brain; RT-PCR	increase of mRNA expression by 35%		[72]
Rat	**CYP27B1**	Environmental impact	Cesium contamination	chronic exposure with post-accidental doses of ^{137}Cs in drinking water for 3 months, at a dose of 6500 Bq/l (150 Bq/rat/day), kidney; RT-PCR	no significant change of mRNA expression		[72]
Rat	**CYP27B1**	Environmental impact	Cesium contamination	newborn rats chronically exposed with post-accidental doses of ^{137}Cs in drinking water durin lactation period, at a dose of 6500 Bq/l (150 Bq/rat/day), liver, kidney; RT-PCR	decrease of mRNA expression (by 39%)		[75]
Rat	**CYP27B1**	Environmental impact	Uranium contamination	single acute depleted uranium (as uranyl nitrate) intragastric administration (204 mg/kg body weight dissolved in 1.5 ml), kidney; RT-PCR	increase of mRNA expression at days 1 and 3 after treatment (11- and 4-fold respectively)		[73]
Rat	**CYP27B1**	Environmental impact	Uranium contamination	chronic contamination for 9 months by	no change of mRNA level expression	dose corresponds to the double of	[74]

Species	Enzyme	Category	Effectors	Model; method used	Effects	Remarks	References
				depleted uranium (uranyl nitrate) through drinking water of dose 1 mg/rat/day, kidney, mitochondria; RT-PCR depleted uranium (uranyl nitrate) through drinking water of dose 1 mg/rat/day, kidney, mitochondria; RT-PCR depleted uranium (uranyl nitrate) through drinking water of dose 1 mg/rat/day, kidney, mitochondria; RT-PCR depleted uranium (uranyl nitrate) through drinking water of dose 1 mg/rat/day, kidney, mitochondria; RT-PCR depleted uranium (uranyl nitrate) through drinking water of dose 1 mg/rat/day, kidney, mitochondria; RT-PCR depleted uranium (uranyl nitrate) through drinking water of dose 1 mg/rat/day, kidney, mitochondria; RT-PCR			
Rat	**CYP2A**	Environmental impact	Uranium contamination	chronically exposed to depleted uranium (as uranyl nitrate) in drinking water, 1 mg/(rat day) for 9 months, liver microsomes; testosterone 7α-hydroxylase activity	no change in hepatic activity		[60]
Rat	**CYP2B**	Environmental impact	Uranium contamination	chronically exposed to depleted uranium (as uranyl nitrate) in drinking water, 1 mg/(rat day) for 9 months, liver microsomes; testosterone 16α-hydroxylase activity	no change in hepatic activity		[60]
Rat	**CYP2B**	Environmental impact	UV irradiation	liver, UVB irradiation; ADM activity	no change of activity		[65]
Rat	**CYP2B1**	Environmental impact	Uranium contamination	uranyl nitrate solution injected once via the tail vein (5 mg/kg), liver, microsomes; Western blotting, Northern blotting	no change of protein or mRNA expression	induced acute renal failure observed	[67,68,69,70,71]
Rat	**CYP2B1**	Environmental impact	Uranium contamination	chronically exposed to depleted uranium (as uranyl nitrate) in drinking water, 1 mg/(rat day) for 9 months, brain, liver, lung, kidney, intestine; RT-PCR	increase of mRNA expression in kidney		[60]
Rat	**CYP2B2**	Environmental impact	Uranium contamination	uranyl nitrate solution injected once via the tail vein (5 mg/kg), liver, microsomes; immunoblotting, mRNA blotting	no change of protein or mRNA expression	induced acute renal failure observed	[67,68,69,70,71]
Rat	**CYP2C**	Environmental impact	Uranium contamination	chronically exposed to depleted uranium (as uranyl nitrate) in drinking water, 1 mg/(rat day) for 9 months,	no change in hepatic activity		[60]

Species	Enzyme	Category	Effectors	Model; method used	Effects	Remarks	References
				liver microsomes; testosterone 2 liver microsomes; testosterone 2 hydroxylase activity			
Rat	**CYP2C11**	Environmental impact	Uranium contamination	uranyl nitrate solution injected once via the tail vein (5 mg/kg), liver, microsomes; immunoblotting, mRNA blotting	decrease of protein level to 20% and mRNA expression to 25% of control	induced acute renal failure observed	[67,68,69,70,71]
Mice	**CYP2E1**	Environmental impact	Fast neutron irradiation	whole body fast neutron irradiation of 0, 0.25, 1, 2, 4 and 8 Gy, liver samples, hepatocytes; histopathology, immunohistochemistry	dose-dependent increase of protein expression		[78]
Mice	**CYP2E1**	Environmental impact	γ-radiation, γ-rays	low doses of continuous γ-radiation, liver;	decreased mRNA expression and protein levels		[79]
Mice	**CYP2E1**	Environmental impact	γ-radiation, γ-rays	low doses of acute γ-radiation, liver;	increased protein level, decreased mRNA expression		[79]
Mice	**CYP2E1**	Environmental impact	γ-radiation, γ-rays	high doses of acute γ-radiation, liver;	decreased protein level, decreased mRNA expression		[79]
Mice	**CYP2E1**	Environmental impact	γ-radiation, γ-rays	low intensity gamma-radiation and ethanol combined administration, liver;	protein level increased in the first week, back to normal on second week	changes of CYP2E1 protein amount at the end of the fifth week accompanied by a decrease of CYP2E1 mRNA level	[80]
Rat	**CYP2E1**	Environmental impact	γ-radiation, γ-rays	whole body irradiation of 3 gray (G) at a dosage rate of 12.5 cG:min from a ^{60}Co radiation source, liver; immunoblotting, mRNA blotting	increased mRNA (3.6-fold) and protein (2.5-fold) expression at 24 h		[66]
Rat	**CYP2E1**	Environmental impact	γ-radiation, γ-rays	whole body irradiation of 3 gray (G) at a dosage rate of 12.5 cG/min from a ^{60}Co radiation source; chlorzoxazone pharmacokinetics i.v.	significantly greater plasma concentration-time curve and the amount of 6-hydroxychlorzoxazone excreted in 8 h urine		[66]

Species	Enzyme	Category	Effectors	Model; method used	Effects	Remarks	References
Rat	**CYP2E1**	Environmental impact	γ-radiation, γ-rays	whole body irradiation of 0.5–1 gray (G) at a dosage rate of 12.5 cG/min from a ^{60}Co radiation source, liver, microsomes; immunoblotting, mRNA blotting	no change of mRNA expression		[66]
Rat	**CYP2E1**	Environmental impact	γ-radiation, γ-rays	whole body irradiation of 3–9 gray (G) at a dosage rate of 12.5 cG/min from a ^{60}Co radiation source, liver microsomes	small but significant increase mRNA expression at 24 h than those irradiated at a single dose of 3 G g-rays	liver injury observed	[66]
Rat	**CYP2E1**	Environmental impact	Uranium contamination	uranyl nitrate solution injected once via the tail vein (5 mg/kg), plasma, liver, microsomes; chlorzoxazone CZX pharmacokinetics i.v., microsomal metabolism, immunoblotting, mRNA blotting	increase of protein level 2.3 times and mRNA expression 3 times, increase of activity	induced acute renal failure, subcutaneous injection of rHGH for one day on the fourth day after uranyl nitrate or glucose (dissolved drinking water for 5 days) reduced the expression of CYP2E1	[67,68,69,70,71]
Rat	**CYP2R1**	Environmental impact	Cesium contamination	chronic exposure with post-accidental doses of 1^{37}Cs in drinking water for 3 months, at a dose of 6500 Bq/l (150 Bq/rat/day), liver; RT-PCR	increase of mRNA expression (by 40%)		[72]
Rat	**CYP2R1**	Environmental impact	Cesium contamination	chronic exposure with post-accidental doses of ^{137}Cs in drinking water for 3 months, at a dose of 6500 Bq/l (150 Bq/rat/day), brain; RT-PCR	decrease of mRNA expression (by 20%)		[72]
Rat	**CYP2R1**	Environmental impact	Cesium contamination	newborn rats chronically exposed with post-accidental doses of ^{137}Cs in drinking water during lactation period, at a dose of 6500 Bq/l (150 Bq/rat/day), liver, kidney; RT-PCR	decrease of mRNA expression (by 26%)		[75]

Species	Enzyme	Category	Effectors	Model; method used	Effects	Remarks	References
Rat	**CYP2R1**	Environmental impact	Uranium contamination	single acute depleted uranium (as uranyl nitrate) intragastric administration (204 mg/kg body weight dissolved in 1.5 ml), liver, mitochondria; RT-PCR, activity ([4-^{14}C]cholesterol as substrate)	no gross modifications in the expression, slight increase of mRNA expression at day 3 after treatment		[73]
Rat	**CYP3A**	Environmental impact	γ-radiation, γ-rays	whole body irradiation of 3 gray (G) at a dosage rate of 12.5 cG/min from a ^{60}Co radiation source, liver, microsomes; immunoblotting, mRNA blotting	no change in the mRNA expression at 24 h		[66]
Rat	**CYP3A**	Environmental impact	Uranium contamination	chronically exposed to depleted (as uranyl nitrate) in drinking water, 1 mg/(rat day) for 9 months, liver microsomes; testosterone 6β-hydroxylation activity	no change in hepatic activity		[60]
Rat	**CYP3A**	Environmental impact	Uranium contamination	single subcutaneous administration of depleted uranium, sublethal toxic dose of 11.5 mg/kg, liver, microsomes; testosterone 6β-hydroxylation activity	decrease of activity at day 1 but returned to levels similar to controls at day 3		[59]
Rat	**CYP3A**	Environmental impact	UV irradiation	liver, UVB irradiation; EMDM activity	no change of activity		[65]
Rat	**CYP3A**	Environmental impact	UV irradiation	skin, AVA and UVB irradiation; EROD activity	induction of activity		[65]
Rat	**CYP3A1**	Environmental impact	Uranium contamination	chronically exposed to depleted (as uranyl nitrate) in drinking water, 1 mg/(rat day) for 9 months, brain, liver, lung, kidney, intestine; RT-PCR	increase of mRNA expression in brain, liver, and kidney	stimulatory effect might lead to hepatic or extrahepatic toxicity (or both) during drug treatment	[60]
Rat	**CYP3A1**	Environmental impact	Uranium contamination	single subcutaneous administration of	increase in expression of mRNA 3 days after		[59]

Species	Enzyme	Category	Effectors	Model; method used	Effects	Remarks	References
				depleted uranium (as uranyl nitrate) sublethal toxic dose of 11.5 mg/kg, liver, microsomes; RT-PCR depleted uranium (as uranyl nitrate) sublethal toxic dose of 11.5 mg/kg, liver, microsomes; RT-PCR depleted uranium (as uranyl nitrate) sublethal toxic dose of 11.5 mg/kg, liver, microsomes; RT-PCR depleted uranium (as uranyl nitrate) sublethal toxic dose of 11.5 mg/kg, liver, microsomes; RT-PCR depleted uranium (as uranyl nitrate) sublethal toxic dose of 11.5 mg/kg, liver, microsomes; RT-PCR			
Rat	**CYP3A2**	Environmental impact	Uranium contamination	chronically exposed to depleted (as uranyl nitrate) in drinking water, 1 mg/(rat day) for 9 months, brain, liver, lung, kidney, intestine; RT-PCR	increase of mRNA expression in lungs and liver	stimulatory effect might lead to hepatic or extrahepatic toxicity (or both) during drug treatment	[60]
Rat	**CYP3A2**	Environmental impact	Uranium contamination	single subcutaneous administration of depleted uranium (as uranyl nitrate) sublethal toxic dose of 11.5 mg/kg, liver, microsomes; RT-PCR	no change in expression of mRNA		[59]
Rat	**CYP3A2**	Environmental impact	Uranium contamination	uranyl nitrate solution injected once via the tail vein (5 mg/kg), liver, microsomes; immunoblotting, mRNA blotting	no change of protein or mRNA expression	induced acute renal failure observed	[68,71]
Rat	**CYP3A23**	Environmental impact	Uranium contamination	uranyl nitrate solution injected once via the tail vein (5 mg/kg), liver, microsomes; immunoblotting, mRNA blotting	increase of protein level 4 times, no change of mRNA expression	induced acute renal failure observed	[67,68,69,70]
Rat	**CYP46A1**	Environmental impact	Uranium contamination	chronic contamination for 9 months by depleted uranium (uranyl nitrate) through drinking water of dose 1 mg/rat/day, brain; RT-PCR	increase of mRNA expression by 39%	dose corresponds to the double of highest concentration found naturally in Finland	[36]
Human	**CYP4A11**	Environmental impact	UV irradiation	keratinocytes, UVA irradiation, microsomes; gel electrophoresis, RT-PCR, immunoblotting, thin-layer chromatography	mRNA expression detected	mRNA was not detected in any keratinocyte preparations under control conditions, proposed that CYP4A11 may participate in the defense mechanism against UVA-induced oxidative damage	[8]

Species	Enzyme	Category	Effectors	Model; method used	Effects	Remarks	References
Human	**CYP4A11**	Environmental impact	UV irradiation	keratinocytes, combined UVA and UVB or UVA irradiation, microsomes; gel electrophoresis, RT-PCR, immunoblotting, thin layer chromatography	induction of mRNA and protein	mRNA was not detected in any keratinocyte preparations under control conditions, proposed that CYP4A11 may participate in the defense mechanism against UVA-induced oxidative damage	[8]
Human	**CYP4A11**	Environmental impact	UV irradiation	keratinocytes, UVB irradiation, microsomes; gel electrophoresis, RT-PCR	mRNA not detected		[8]
Rat	**CYP7A1**	Environmental impact	Cesium contamination	chronic exposure with post-accidental doses of ^{137}Cs in drinking water for 3 months, at a dose of 6500 Bq/l (150 Bq/rat/day), liver, microsomes; quantitative RT-PCR, activity with [4-^{14}C]Cholesterol as substrate	no change in expression of mRNA and activity		[37,96]
Rat	**CYP7A1**	Environmental impact	Uranium contamination	single subcutaneous administration of depleted uranium (as uranyl nitrate) sublethal toxic dose of 11.5 mg/kg, liver, microsomes; [4-^{14}C]cholesterol 7α-hydroxyase activity	no significant change in the activity		[59]
Rice	**CYP84A**	Environmental impact	UV irradiation	UVB or UVC irradiation on 1- and 2-week-old plants for 6 hours; semiquantitative RT-PCR	increase of gene expression under UVB and UVC irradiation	protection against damage due to UV irradiation proposed	[76]
Rat	**CYP27A1**	Environmental impact	Cesium contamination	chronic exposure with post-accidental doses of ^{137}Cs in drinking water for 9 months, at a dose of 6500 Bq/l (150 Bq/rat/day), brain; RT-PCR	decrease of mRNA expression	plasma profile, and brain and liver cholesterol concentrations were unchanged	[77]

Species	Enzyme	Category	Effectors	Model; method used	Effects	Remarks	References
Rat	**CYP7A1**	Environmental impact	Uranium contamination	low-level chronic ingestion of depleted uranium in drinking water for 9 months, 40 mg/kg, liver; RT-PCR, specific activity	decrease of the activity		[39]
Rat	**CYP7B1**	Environmental impact	Uranium contamination	low-level chronic ingestion of depleted uranium in drinking water for 9 months, 40 mg/kg, liver; RT-PCR, specific activity	decrease of expression		[39]

Table 3

Effects of Ionizing and Non-ionizing Irradiation on Expression and Activity of Oxidative Stress and Other Enzymes

Species	Enzyme	Category	Effectors	Model; method used	Effects	Remarks	References
Rat	**ACO (aconitase)**	Environmental impact	γ-radiation, γ-rays	whole body irradiation of 3 and 9 gray (G) at a dosage rate of 12.5 cG/min from a ^{60}Co radiation source, liver, mitochondrial post-nuclear fraction; conversion of citrate to isocitrate	activity decreased 30–90% by increasing gamma-irradiation		[66]
Human	**ALPL (alkaline phosphatase)**	Environmental impact	γ-radiation, γ-rays	workers exposed to short-life radioactive isotopes ^{131}I and ^{99}Tc, blood smears;	decreased activity		[87]
Human	**APRT (adenyl phosphoribosyl transferase)**	Clinical impact	γ-radiation, γ-rays	single dose of 1-Gy 137Cs-gamma-rays, TK6 lymphoblastoid cells; two-dimensional (2-D) gel electrophoresis, MALDI-TOF, immunoblotting	decreased protein level		[88]
Guinea pigs	**CAT (catalase)**	Environmental impact	γ-radiation, γ-rays	irradiated with the doses of 8 Gy or 15 Gy, single dose/whole body, ^{60}Co, source axis distance 80 cm, liver; activity	activity decreased at 15 Gy		[83]
Mice	**CAT (catalase)**	Clinical impact	γ-radiation, γ-rays	whole body irradiation of mice with Ehrlich solid tumors irradiated with different doses of γ-rays (0–9 Gy) at a dose rate of 0.0153 Gy/s, solid tumor; activity measured as decomposition of H_2O_2 at 240 nm	no activity detected in control or irradiated samples		[56]
Mice	**CAT (catalase)**	Clinical impact	γ-radiation, γ-rays	whole body irradiated mice with Ehrlich solid tumor in the thigh pad and non-tumor bearing animals, irradiated with different doses of gamma-radiation (0–9 Gy) at a dose rate of 0.0153 Gy/s, liver; activity measured as decomposition of H2O2 at 240 nm	activity decreased with dose in tumor and non-tumor mice, activity was higher in liver of tumor mice than control		[81]
Rat	**CAT (catalase)**	Environmental impact	γ-radiation, γ-rays	whole body single dose of γ-radiation (5 Gy); testicular level	decreased protein level	supplementation with extract of Xylopia aethiopica and vitamin C reversed the effect	[82]
Mice	**CAT (catalase)**	Environmental impact	UV irradiation	Skh:HR-1 hairless mice, in vivo, single UVB irradiation; activity assays	decrease of activity by 12 h after irradiation		[86]
Mice	**NADPH-quinone reductase**	Clinical impact	γ-radiation, γ-rays	whole body irradiation of mice with Ehrlich solid tumors irradiated with different doses of γ-rays (0–9 Gy) at a dose rate of 0.0153 Gy/s, solid tumor; activity measured as reduction of 2,6-dichlorophenolindophenol	activity increased with increase in radiation dose, at 9 Gy it was about 50% higher compared to the unirradiated control		[56]
Mice	**NADPH-quinone reductase**	Clinical impact	γ-radiation, γ-rays	whole body irradiated mice with Ehrlich solid tumor in the thigh pad and non-tumor bearing animals, irradiated with different doses of γ-radiation (0–9 Gy) at a dose rate of 0.0153 Gy/s, liver; activity measured as reduction of 2,6-dichlorophenolindophenol	activity increased at all doses except 9 Gy, activity higher in liver of tumor compared to non-tumor bearing mice		[81]

Species	Enzyme	Category	Effectors	Model; method used	Effects	Remarks	References
Mice	**NADPH-quinone reductase**	Environmental impact	γ-radiation, Gamma-rays	whole body irradiation, different doses of gamma-rays at 1.38 Gy/min, liver; activity	activity increased up to 5 Gy and decreased thereafter	administration of phenothiazines increased the radiation effect at lower doses providing the radioprotective action	[55]
Mice	**GLY I (glyoxalase I)**	Clinical impact	γ-radiation, γ-rays	whole body irradiation of mice with Ehrlich solid tumors irradiated with different doses of γ-rays (0–9 Gy) at a dose rate of 0.0153 Gy/s, solid tumor; activity measured as formation of (*S*)-D-lactoylglutathione	increased activity with increase in radiation dose		[56]
Mice	**GLY I (glyoxalase I)**	Clinical impact	γ-radiation, γ-rays	whole body irradiated mice with Ehrlich solid tumor in the thigh pad and non-tumor bearing animals, irradiated with different doses of gamma-radiation (0–9 Gy) at a dose rate of 0.0153 Gy/s, liver; activity measured by formation of (*S*)-D-lactoylglutathione	increased activity in both normal and tumor-bearing animals from 1–4 Gy in a dose dependent manner, declined beyond 4 G, activity higher in liver of tumor-bearing compared to non-tumor bearing mice		[81]
Guinea pigs	**GPX (glutathione peroxidase)**	Environmental impact	γ-radiation, γ-rays	irradiated with the doses of 8 Gy or 15 Gy, single dose/whole body, ^{60}Co, source axis distance 80 cm, liver; activity	activity increased at 15 Gy		[83]
Human	**GPX (glutathione peroxidase)**	Clinical impact	Ionizing irradiation	tumor cell lines (MCF-7, LXF and Sk-Mel), single doses (5, 10, and 20 Gy);	no significant change of mRNA expression		[42]
Mice	**GST (glutathione transferase)**	Clinical impact	γ-radiation, γ-rays	whole body irradiation of mice with Ehrlich solid tumors irradiated with different doses of gamma rays (0–9 Gy) at a dose rate of 0.0153 Gy/s, solid tumors activity measured as formation of GSHCDNB (1-chloro-2,4-dinitrobenzene) conjugate, Western blotting	increased activity between 4 an 9 Gy, dose dependent increase of protein level compared to control tissue		[56]
Mice	**GST (glutathione transferase)**	Clinical impact	γ-radiation, γ-rays	whole body irradiated mice with Ehrlich solid tumor in the thigh pad and non-tumor bearing animals, irradiated with different doses of gamma-radiation (0–9 Gy) at a dose rate of 0.0153 Gy/s, liver; activity expressed as 1-chloro-2,4-dintrobenzene conjugate formed, Western blotting	increased activity depending on the dose of radiation in both normal and tumor-bearing animals		[81]
Mice	**GST (glutathione transferase)**	Environmental impact	γ-radiation, γ-rays	whole body irradiation, different doses of γ-rays at 1.38 Gy/min, liver; activity	activity increased up to 5 Gy and decreased thereafter	administration of phenothiazines increased the radiation effect at lower doses providing the radio protective action	[55]
Mice	**GST (glutathione transferase)**	Environmental impact	γ-radiation, γ-rays	whole body treatment at the dose of 8 and 9 Gy	increase of mRNA expression	2-(allylthio)pyrazine pretreatment (100 mg/kg/day, for 2 days) prior to whole body irradiation increased the 30 day survival rate of mice to 91%	[89]

Species	Enzyme	Category	Effectors	Model; method used	Effects	Remarks	References
Rat	**GST (glutathione transferase)**	Environmental impact	γ-radiation, γ-rays	whole body treatment with either 3 or 0.5 Gy of radiation/day, dosage of 12.5 cGy/min from a ^{60}Co radiation source, liver; immunoblotting, mRNA blotting, scanning densitometry	decreased mRNA expression at 3 and 8 hr after irradiation, followed by increase of mRNA level by 2-fold at 15 and 24 hr after irradiation and return to the levels of untreated rats at 48 hr after treatment, paralleled changes of protein levels with those of mRNA	oltipraz pretreatment before irradiation resulted in additional increase of mRNA expression and increased the survival rate, protective role of oltipraz suggested	[90]
Rat	**GST (glutathione transferase)**	Environmental impact	γ-radiation, γ-rays	whole body single dose of γ-radiation (5 Gy), testicular level; protein level	decrease of protein level	supplementation with extract of *Xylopia aethiopica* and vitamin C reversed the effect	[82]
Rat	**GST (glutathione S-transferase)**	Clinical impact	Ionizing irradiation	preliminary radiation-exposed, transplanted Guerin's carcinoma, liver, microsomes	decreased activity in the latent and logarithmic phases of oncogenesis, no effect on terminal stages of Guerin's carcinoma growth		[57]
Human	**GST (glutathione transferase)**	Environmental impact	Radioactivity-contaminated areas	placental samples at term, cytosolic fraction; activity measured as GSH conjugation with 1-chloro-2,4 dinitrobenzene	down-regulation of activity and mRNA level in samples exposed to highest levels of radioactivity	imbalance in detoxification capacity suggested	[54]
Rat	**GST (glutathione transferase)**	Clinical impact	X-rays	preliminary radiation-exposed rats with Guerin's carcinoma, liver, microsomal fraction; activity	reduced activity		[57]
Rat	**GSTA2-2 (glutathione transferase A2-2)**	Environmental impact	γ-radiation, γ-rays	whole body treatment with either 3 or 0.5 Gy of radiation/day, dosage of 12.5 cGy/min from a ^{60}Co radiation source, liver; immunoblotting, mRNA blotting, scanning densitometry	increase of mRNA level (threefold) after 3 Gy g-irradiation	dexamethasone prior to 3 Gy irradiation exhibited 80%–93% suppression in the radiation-inducible increases in the mRNA level and **reduced the mean survival time**	[91]
Rat	**GSTA2-2 (glutathione transferase A2-2)**	Environmental impact	γ-radiation, γ-rays	whole body treatment at the dose of 8 Gy, liver; mRNA blotting	increase of mRNA expression 2- to 2.8-fold	2-(allylthio)pyrazine pretreatment mRNA expression at 24 h after 2-AP treatment	[89]
Mice	**GSTA3-2 (glutathione transferase A3-3)**	Environmental impact	γ-radiation, γ-rays	whole body treatment at the dose of 8 Gy, liver; mRNA blotting	increase of mRNA expression	2-(allylthio)pyrazine pretreatment increased mRNA expression	[89]
Rat	**GSTA3-3 (glutathione transferase alpha3)**	Environmental impact	γ-radiation, γ-rays	whole body treatment with either 3 or 0.5 Gy of radiation/day, dosage of 12.5 cGy/min from a ^{60}Co radiation source, liver; immunoblotting, mRNA blotting, scanning densitometry	increase of mRNA level (3-fold) after 3 Gy g-irradiation	dexamethasone prior to 3 Gy irradiation exhibited 80%–93% suppression in the radiation-inducible increases in the mRNA level and reduced the mean survival time	[91]
Rat	**GSTA3-3 (glutathione transferase A3-3)**	Environmental impact	γ-radiation, γ-rays	whole body treatment at the dose of 8 Gy, liver; mRNA blotting	increase of mRNA expression	2-(Allylthio)pyrazine pretreatment caused smaller	[89]

Species	Enzyme	Category	Effectors	Model; method used	Effects	Remarks	References
						increase mRNA expression at 24 h after 2-AP treatment	
Rat	**GSTA5-5 (glutathione transferase A5-5)**	Environmental impact	γ-radiation, γ-rays	whole body treatment with either 3 or 0.5 Gy of radiation/day, dosage of 12.5 cGy/min from a ^{60}Co radiation source, liver; immunoblotting, mRNA blotting, scanning densitometry	increase of mRNA level (3-fold) after 3 Gy g-irradiation	dexamethasone prior to 3 Gy irradiation exhibited 80%–93% suppression in the radiation-inducible increases in the mRNA level and reduced the mean survival time	[91]
Rat	**GSTA5-5 (glutathione transferase A5-5)**	Environmental impact	γ-radiation, γ-rays	whole body treatment at the dose of 8 Gy, liver; mRNA blotting	increase of mRNA expression	2-(allylthio)pyrazine pretreatment caused smaller increase mRNA expression at 24 h after treatment	[89]
Rat	**GSTM1-1 (glutathione transferase M1-1)**	Environmental impact	γ-radiation, γ-rays	whole body treatment with either 3 or 0.5 Gy of radiation/day, dosage of 12.5 cGy/min from a ^{60}Co radiation source, liver; immunoblotting, mRNA blotting, scanning densitometry	increase of mRNA level (3-fold) after 3 Gy g-irradiation	dexamethasone prior to 3 Gy irradiation at doses of 1 mg/kg exhibited 68% suppression in the radiation-inducible increases in the mRNA level	[91]
Rat	**GSTM1-1 (glutathione transferase M1-1)**	Environmental impact	γ-radiation, γ-rays	whole body treatment at the dose of 8 Gy, liver; mRNA blotting	increase of mRNA expression	2-(allylthio)pyrazine pretreatment caused smaller increase mRNA expression at 24 h after treatment	[89]
Rat	**GSTM2-2 (glutathione transferase M2-2)**	Environmental impact	γ-radiation, γ-rays	whole body treatment with either 3 or 0.5 Gy of radiation/day, dosage of 12.5 cGy/min from a ^{60}Co radiation source, liver; immunoblotting, mRNA blotting, scanning densitometry	no significant change in mRNA level after 3 Gy g-irradiation	dexamethasone prior to 3 Gy irradiation exhibited no significant change in mRNA level	[91]
Rat	**GSTM2-2 (glutathione transferase M2-2)**	Environmental impact	γ-radiation, γ-rays	whole body treatment at the dose of 8 Gy, liver; mRNA blotting	increase of mRNA expression	2-(allylthio)pyrazine pretreatment caused smaller increase mRNA expression at 24 h after treatment	[89]
Human	**GSTO1-1 (glutathione transferase O1-1)**	Clinical impact	γ-radiation, γ-rays	single dose of 1-Gy ^{137}Cs-gamma-rays, TK6 lymphoblastoid cells; two-dimensional (2D) gel electrophoresis, MALDI-TOF, immunoblotting	no change in protein level		[88]
Mice	**GSTP1-1 (glutathione transferase P1-1)**	Environmental impact	γ-radiation, γ-rays	whole body treatment at the dose of 8 Gy, liver; mRNA blotting	increase of mRNA expression	no influence of 2-(allylthio)pyrazine pretreatment	[89]
Human	**GSTP1-1 (glutathione transferase P1-1)**	Clinical impact	Ionizing irradiation	tumor cell lines (MCF-7, LXF and Sk-Mel), single doses (5, 10 and 20 Gy);	increase of mRNA expression		[42]
Human	**GSTP1-1 (glutathione transferase P1-1)**	Clinical impact	Ionizing irradiation	fractionated X-irradiation of AuxB1Chinese hamster ovary cell lines; Western blotting	increase of **protein** expression		[30]
Murine	**GSTP1-1 (glutathione transferase P1-1)**	Clinical impact	Ionizing irradiation	NIH 3T3 cells treated with single doses of 5, 10 and 20 Gy	increase of mRNA expression and protein level		[45]

Species	Enzyme	Category	Effectors	Model; method used	Effects	Remarks	References
Murine	**GSTP1-1 (glutathione transferase P1-)**	Clinical impact	Ionizing irradiation	human lung carcinoma cell line LXF 289, single doses of 5, 10, and 20 Gy	increase of mRNA expression and protein level		[45]
Mice	**LDH (L-lactate dehydrogenase)**	Clinical impact	γ-radiation, γ-rays	whole body irradiation of mice with Ehrlich solid tumors irradiated with different doses of gamma rays (0–9 Gy) at a dose rate of 0.0153 Gy/s, solid tumor; activity measured as disappearance of NADH (340 nm)	increased activity up to 6 Gy, declined beyond 6 Gy		[56]
Mice	**LDH (L-lactate dehydrogenase)**	Clinical impact	γ-radiation, γ-rays	whole body irradiated mice with Ehrlich solid tumor in the thigh pad and non-tumor bearing animals, irradiated with different doses of gamma-radiation (0–9 Gy) at a dose rate of 0.0153 Gy/s, liver; activity measured by disappearance of NADH (340 nm)	increased activity at lower doses (2 and 4 Gy), declined at higher doses (6–9 Gy) in both normal and tumor-bearing animals		[81]
Mice	**LDH (L-lactate dehydrogenase)**	Environmental impact	γ-radiation, γ-rays	whole body irradiation, different doses of gamma- rays at 1.38 Gy/min, liver; activity	progressive increase in activity	administration of phenothiazines inhibited activity	[55]
Mice	**LDH (L-lactate dehydrogenase)**	Environmental impact	γ-radiation, γ-rays	whole body irradiation, different doses of gamma radiation (1–9 Gy) at a dose rate of 0.023 Gy/s, liver activity	activity increased at doses above 3 Gy	phenylmethylsulfonyl fluoride inhibited activity, dithiothreitol inhibited the release of lactate dehydrogenase	[92,93]
Mice	**mEH (microsomal epoxide hydrolase)**	Environmental impact	γ-radiation, γ-rays	whole body treatment at the dose of 0.5 and 8 Gy, liver; mRNA blotting	increase of mRNA expression 2- to 2.8-fold	2-(allylthio)pyrazine pretreatment mRNA expression at 24 h after 2-AP treatment	[89]
Rat	**mEH (microsomal epoxide hydrolase)**	Environmental impact	γ-radiation, γ-rays	whole body treatment with either 3 or 0.5 Gy of radiation/day, dosage of 12.5 cGy/min from a ^{60}Co radiation source, liver; immunoblotting, mRNA blotting, scanning densitometry	increase of mRNA level (threefold) after 3 Gy g-irradiation	dexamethasone prior to 3 Gy irradiation exhibited 80%–93% suppression in the radiation-inducible increases in the mRNA level and reduced the mean survival time	[91]
Rat	**mEH (microsomal epoxide hydrolase)**	Environmental impact	γ-radiation, γ-rays	whole body single dose (3 Gy) treatment, liver; immunoblotting	mRNA level transiently decreased at 3 and 8 h after irradiation, increased 3- to 4-fold at 15 to 48 h post-irradiation, returning to the level in untreated animals at 72 h, paralleled changes of protein levels with those of mRNA	mRNA level increased by oltipraz treatment	[97]
Human	**MGMT (O^6-alkylguanine-DNA alkyltransferase)**	Clinical impact	Ionizing irradiation	tumor cell lines (MCF-7, LXF, and Sk-Mel), single doses (5, 10, and 20 Gy);	no significant change of mRNA expression		[42]
Human	**MPO (myeloperoxydase)**	Environmental impact	γ-radiation, γ-rays	workers exposed to short-life radioactive isotopes ^{131}I and ^{99}Tc, blood smears; stained for L-ALP and MPO and benzidine method	decreased activity		[87]

Species	Enzyme	Category	Effectors	Model; method used	Effects	Remarks	References
Human	**PP1α1 (serine/threonine protein phosphatase PP1-α1)**	Clinical impact	γ-radiation, γ-rays	single dose of 1-Gy ^{137}Cs- gamma-rays, TK6 lymphoblastoid cells; two-dimensional gel electrophoresis, MALDI-TOF, immunoblotting	decreased protein level		[88]
Guinea pigs	**SOD (superoxide dismutase)**	Environmental impact	γ-radiation, γ-rays	irradiated with the doses of 8 Gy or 15 Gy, single dose/whole body, ^{60}Co, source axis distance 80 cm, liver; activity	activity decreased at 15 Gy		[83]
Mice	**SOD (superoxide dismutase)**	Clinical impact	γ-radiation, γ-rays	whole body irradiation of mice with Ehrlich solid tumors irradiated with different doses of gamma rays (0–9 Gy) at a dose rate of 0.0153 Gy/s, solid tumor; activity measured as inhibition of autoxidation of pyrogallol	increased activity with dose up to 4 Gy and then declined beyond 4 Gy at 24 h after irradiation		[56]
Mice	**SOD (superoxide dismutase)**	Clinical impact	γ-radiation, γ-rays	whole body irradiated mice with Ehrlich solid tumor in the thigh pad and non-tumor bearing animals, irradiated with different doses of gamma-radiation (0–9 Gy) at a dose rate of 0.0153 Gy/s, liver; activity measured as inhibition of autoxidation of pyrogallol	activity increased with radiation dose in the liver of tumor-bearing animals, in the liver of normal animals the activity was increased up to 6 Gy and inhibited thereafter, higher activity in liver of tumor-bearing compared to non-tumor bearing mice		[81]
Mice	**SOD (superoxide dismutase)**	Environmental impact	γ-radiation, γ-rays	whole body irradiation, different doses of gamma- rays at 1.38 Gy/min, liver; activity	activity increased up to 5 Gy and decreased thereafter	administration of phenothiazines increased the radiation effect at lower doses providing the radioprotective action	[55]
Rat	**SOD (superoxide dismuase)**	Environmental impact	γ-radiation, γ-rays	whole body single dose (5 Gy) treatment, testis; testicular level	decreased protein level	supplementation with extract of *Xylopia aethiopica* and vitamin C reversed the adverse effects of radiation	[82]
Human	**SOD (superoxide dismutase)**	Environmental impact	Ionizing irradiation	medical workers exposed to occupational low-level doses, plasma samples; activity measured spectrophotometrically	higher SOD activity in the blood samples of exposed vs. unexposed persons	higher activity at occupational doses provide protection against the increased production of reactive oxygen species (ROS)	[84]
Human	**SOD (superoxide dismutase)**	Environmental impact	Ionizing irradiation	blood samples irradiated by 2Gy of gamma radiation, dose-rate 0.45 Gy/min, and the distance from the source of 74 cm; SOD activity measured spectrophotometrically	decrease of SOD activity after high dose irradiation	dysfunction of mitochondrial system suggested at higher doses	[84]
Human	**SOD1 (superoxide dismutase)**	Environmental impact	UV irradiation	epidermis, in vivo, chronic UVB irradiation; activity	increase of activity		[85]
Murine	**SOD1 (superoxide dismutase)**	Environmental impact	UV irradiation	Skh:HR-1 hairless mice, in vivo, single UVB irradiation; activity	decrease of activity by 12 h after irradiation		[86]

Species	Enzyme	Category	Effectors	Model; method used	Effects	Remarks	References
Zebrafish	**SOD1 (superoxide dismutase)**	Environmental impact	UV irradiation	embryos exposed for varying time to UVB on two consecutive days; spectophotometry, RT-PCR	increase of mRNA expression		[9]
Human	**TOP2A (topoisomerase (DNA) IIα)**	Clinical impact	Ionizing irradiation	tumor cell lines (MCF-7, LXF, and Sk-Mel), single doses (5, 10, and 20 Gy);	increases of mRNA expression		[42]
Human	**TYMS (thymidylate synthetase)**	Clinical impact	Ionizing irradiation	tumor cell lines (MCF-7, LXF and Sk-Mel), single doses (5, 10 and 20 Gy);	increases of mRNA expression		[42]
Human	**UQCRC1 (ubiquinol-cytochrome *c* reductase core protein I)**	Clinical impact	γ-radiation, γ-rays	single dose of 1-Gy 137Cs-gamma-rays, TK6 lymphoblastoid cells; two-dimensional (2D) gel electrophoresis, MALDI-TOF, Western blotting	decreased protein level		[88]
Mice	**XDH (xanthine dehydrogenase)**	Environmental impact	γ-radiation, γ-rays	whole body irradiation, different doses of gamma radiation (1–9 Gy) at a dose rate of 0.023 Gy/s, liver; activity	activity decreased at doses above 3 Gy	allopurinol and folic acid inhibited activity, phenylmethylsulfonyl fluoride restored activity	[92,93,94]
Mice	**XOR (xanthine oxidoreductase)**	Environmental impact	γ-radiation, γ-rays	whole body irradiation, different doses of gamma-rays (1–9 Gy) at a dose rate of 0.023 Gy/s or 1.38 Gy/min, liver; activity	activity progressively increased at doses above 3 Gy	phenothiazines, allopurinol, folic acid, and phenylmethylsulfonyl fluoride inhibited activity	[55,92,93,94]
Mice	**XOR (xanthine oxidoreductase)**	Environmental impact	UV irradiation	Skh:HR-1 hairless mice, in vivo, single UVB irradiation; activity	no effect on activity		[86]
Human	**SDH (succinate dehydrogenase)**	Environmental impact	UV irradiation	UV (240–390 nm) irradiation, lymphocytes from human blood donors	photoinactivation immediately after UV-irradiation		[95]
Human	**LDH (L-lactate dehydrogenase)**	Environmental impact	UV irradiation	UV (240–390 nm) irradiation, lymphocytes from human blood donors	photoinactivation immediately after UV-irradiation		[95]
Human	**COX (cytochrome *c* oxidase)**	Environmental impact	UV irradiation	UV (240–390 nm) irradiation, lymphocytes from human blood donors	photoinactivation immediately after UV-irradiation		[95]
Mice	**ChAT (choline acetyl transferase)**	Environmental impact	Uranium contamination	chronic exposure for 8 months by depleted uranium through drinking water 20 mg/l, cerebral cortex; RT-PCR	increase of mRNA level expression by 189%		[38]