Phototoxicity

21

Lars Olof Björn and Pirjo Huovinen

21.1 Introduction

Phototoxicity means that something which is not toxic in itself is converted into a toxin or produces a toxin by the action of light. We can divide phototoxicity into several classes:

Type I phototoxicity arises when a pigment, after absorption of light and acquiring an excited state, either combines directly with an important cell constituent (Fig. 21.1) or transfers electrons or hydrogen atoms. The transfer may take place from or to another molecule, which then becomes a toxic radical or radical ion or produces toxins in subsequent reactions. As an example of the action of a type I phototoxin, we show in Fig. 21.1 how 8-methoxypsoralen (MOPS in medical jargon) combines with thymine residues in DNA.

Type II phototoxicity arises when a pigment (photosensitizer) after absorption of light goes from the excited singlet state to a triplet state, and then reacts with molecular oxygen and produces singlet excited oxygen (see Chap. 1), which is highly toxic.

In some cases, a pigment molecule excited by light absorption transfers an electron to molecular oxygen, thereby producing superoxide anion (see Fig. 21.2). According to the above definitions, this is type I phototoxicity, but in the literature it has also been designated type II phototoxicity, because in practice it is easier to distinguish between oxygen-independent and oxygen-dependent phototoxicity. The main cellular targets of both type I and II phototoxins are DNA, membrane lipids, and membrane proteins. A wide variety of organisms (except those having special protection systems) can be poisoned by most of the substances; that is, they are rather unspecific with regard to poisoned organism.

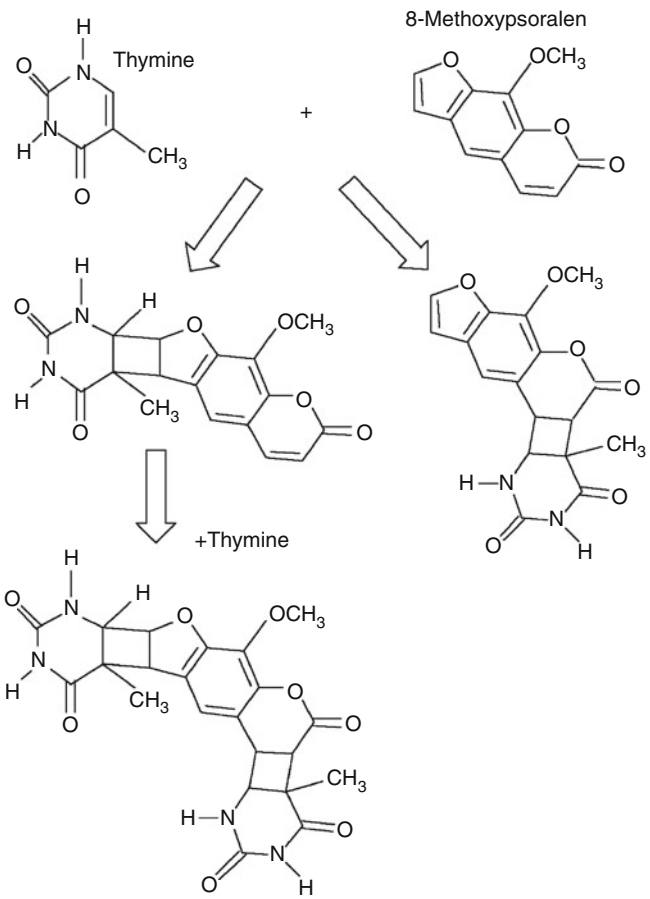

Fig. 21.1 Formation of photoadduct between 8-methoxypsoralen and thymine residues in DNA. The thymine is shown for simplicity as free molecules, but is in reality part of a DNA molecule. One 8-methoxypsoralen molecule can combine with two thymine residues, and if they are bound to opposite DNA strands, cross-bridges can form between the strands. Although "phototoxicity" sounds dangerous, this and other similar reactions are also exploited in phototherapy of certain diseases

L.O. Björn (✉)
School of Life Science, South China Normal University, Guangzhou, China

Department of Biology, Lund University, Lund, Sweden
e-mail: Lars_Olof.Bjorn@biol.lu.se

P. Huovinen
Universidad Austral de Chile, Instituto de Ciencias Marinas y Limnológicas, Valdivia, Chile
e-mail: pirjo.huovinen@uach.cl

L.O. Björn (ed.), *Photobiology: The Science of Light and Life*,
DOI 10.1007/978-1-4939-1468-5_21, © Springer Science+Business Media New York 2015

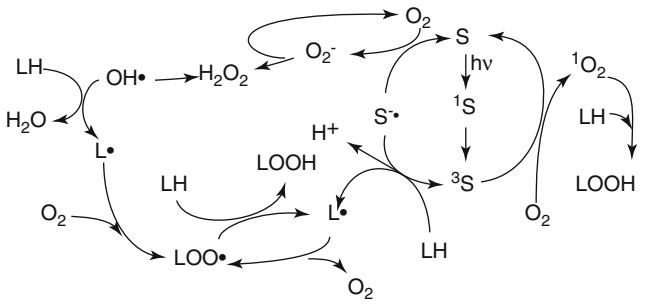

Fig. 21.2 Diagram showing how a pigment (S), excited by light (hυ) via an excited singlet state (^{1}S) to an excited triplet state (^{3}S), can damage a membrane lipid (LH) in several ways (note that the lipid molecules enter the reactions at four points in the diagram). (*1*) Type II reaction (*right part* of the diagram): the triplet pigment may react with triplet (ground state) oxygen (O_2) to form singlet oxygen ($^1O_2$), which can directly convert the lipid to a lipid peroxide (LOOH). (*2*) Classical type I reaction (*lower part* of the diagram): the triplet pigment abstracts a hydrogen atom from the lipid, creating a lipid radical (L•), which combines with triplet oxygen to form a lipid peroxy radical (LOO•). The latter abstracts a hydrogen atom from another lipid molecule to form a lipid peroxide. In this way a new lipid radical is formed, and a chain reaction is created. (*3*) Oxygen-dependent hydrogen abstraction (*upper part* of the diagram): an electron is donated to triplet oxygen, creating superoxide anion, which via formation of hydrogen peroxide and hydroxide radical abstracts hydrogen from the lipid. Also in this case the lipid is degraded to lipid peroxide, and a chain reaction is initiated

As a third type of phototoxicity, we can categorize those cases when a substance is converted into a toxin by a photochemical reaction which does not fall into any of the above categories.

As an example in which several mechanisms contribute to the photodestructive action, we show in Fig. 21.2 a schematic description of how membrane lipids are peroxidized by a photoexcited pigment (see Samadi et al. 2001).

An interesting consequence of lipid peroxidation is that a weak light (ultraweak luminescence) is emitted during the reaction. Lipid peroxidative chain reactions can be initiated also in ways other than through phototoxic action.

In our disposition of the topic "phototoxicity," we shall not follow the categorization into types I and II, but rather subdivide into the different contexts in which phototoxicity has been observed. We shall not include photoallergic reactions here, which, as they involve the immune system, are of a different character. Photoallergy will be treated in Chap. 24.

21.2 Phototoxicity in Plant Defense

The most important defenses of plants against parasites and grazers are of a chemical nature, and among chemical defenses phototoxicity plays an important role, especially among flowering plants. The phototoxic substances employed by plants can also affect people when they appear in food, perfumes, and other cosmetic products and even if we just touch certain plants.

Downum (1992) estimates that 75–100 different phototoxic molecules have been isolated from flowering plants. Phototoxins or phototoxic activity has been reported for about 40 of more than 100 angiosperm families, representing all subclasses except Alismatidae and Arecidae. Many plants have several phototoxic substances. From *Ammi majus* as well as from *Angelica archangelica*, the following ones are reported: angelicin, bergapten, 8-methoxypsoralen, and pimpinellin—from the former one, in addition, furocoumarin and from the latter, one psoralen. The plant family Apiaceae (former name Umbelliferae) dominates the most important cases of phototoxicity of to humans.

The phototoxins affect bacteria, fungi, nematodes, insects, and other organisms. This wide spectrum is due to the fact that the toxins attack cellular constituents common to all cells. DNA is a major target for type I acting chemicals, such as acetophenones, coumarins, furanochromones, furanoquinolines, pterocarpans, and sesquiterpenes. Examples of type II acting compounds are isoquinolines and thiophenes.

Photosensitizers generally have many double bonds, that is, many π-electrons, and most of them are polycyclic. The most common types in plants are acetylenes and furanocoumarins, but many other types also occur.

Since absorption of ultraviolet radiation is a common feature of organic compounds, and absorption for polycyclic systems and acetylenes with conjugated triple bonds (compounds with many π-electrons) extends into the UV-A region, it is not surprising that UV-A (of which there is much more in daylight than of UV-B) in most cases is the most important spectral region for inflicting phototoxicity. However, there are exceptions, and hypericin (present in *Hypericum*, St. John's wort) with its many fused phenyl rings absorbs and is excited to phototoxicity even by yellow and orange light, while some other substances require UV-B radiation. Detailed information on action spectra is still lacking in most cases. Guesses made based on absorption spectra are not reliable, since cases are known in which the phototoxic action takes place with radiation of longer wavelength than that absorbed by the pure substance. The reason for this is probably that the spectrum is shifted when the substance binds to cellular components.

The mode of action of hypericin has been debated, but it has now been established (Delaey et al. 2000) that it required oxygen for phototoxicity. Like several other phototoxic compounds from plants (e.g., psoralen, 8-methoxypsoralen), it has been used in the phototherapy of diseases. Hypericin

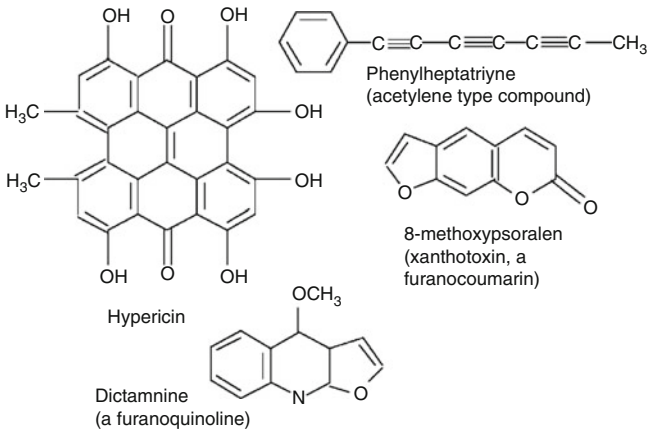

Fig. 21.3 Examples of phototoxic substances from plants

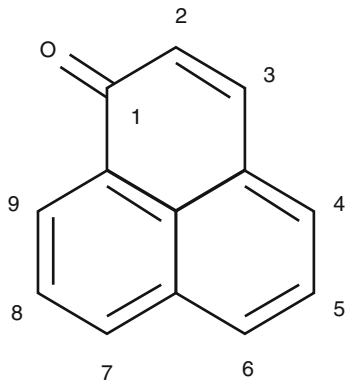

Fig 21.4 Structure of phenalenone in benzene solution

may be particularly dangerous for the lens of the eye (Ehrenshaft et al. 2013).

Specific plant species causing problems for humans and domestic animals naturally vary among countries, but the following are worth mentioning here:

Fig, *Ficus carica*. Fig can be troublesome only for those involved in picking and handling them professionally. One source speculates that fig could have caused trouble for Adam and Eve!

Angelica, *Angelica archangelica*. This and other *Angelica* species are used as traditional medicine from Korea to Lapland and also in drinks. They have caused problems for growers and collectors.

Buckwheat, *Fagopyrum esculentum*. Causes trouble mainly in grazing cattle.

Celery, *Apium graveolens*. Has caused burns when ingested before visiting suntan parlor. Contains 5-methoxypsoralen, 8-methoxypsoralen (xanthotoxin), and 4,5′,8-trimethylpsoralen. Of special interest is that this plant can contain tenfold increased contents of psoralen derivatives after infection with a fungus, *Sclerotinia sclerotium* (pink rot disease). Persons handling celery professionally are at risk. Disease-resistant celery contains increased levels of furocoumarins (Fig. 21.3).

Hogweed (*Heracleum*), especially Russian hogweed (*Heracleum mantegazzianum*). Light produces severe blisters in skin that has been in touch with the plant. The plant has spread over large areas of Europe and North America. *Heracleum* species contain angelicin, bergapten, pimpinellin, 5-methoxypsoralen, and other related substances.

Spring parsley (also erroneously called wild carrot), *Cymopterus watsonii*, growing in Oregon, Nevada, and western Utah. Problems with grazing sheep and cattle. Newborn lambs and calves die because mothers become so touch sensitive that they refuse nursing. The plant contains furocoumarins, 8-methoxypsoralen (xanthotoxin), and bergapten.

Lei flowers, especially *Pelea anisata*. Leis are the greeting wreaths that visitors receive on their arrival to Hawaii.

Burning bush of Moses (also called gas plant), *Dictamnus albus*. The plant grows wild in Europe and Asia and is used as a garden plant also in other parts of the world. It belongs to the family Rutaceae, which harbors also other plants with some phototoxicity, among them *Citrus* species and *Ruta graveolens*, garden rue.

St. John's wort. *Hypericum* species contain hypericin and can cause trouble both to grazing animals and to persons who consume drinks based on *Hypericum* extracts and are exposed to light afterwards.

Some of the phytophototoxins are used for medical treatments. The most noteworthy example is treatment of vitiligo and psoriasis with 8-methoxypsoralen and related substances. In fact, the juice of the Egyptian plant *Ammi majus* has been used for this purpose since 2000 B.C. (Pathak and Fitzpatrick 1992). We can only give some examples of detailed mechanisms of action in phototoxicity. For further information on phototoxic plants and plant phototoxins, see Pathak (1986), Downum (1992), Lovell (1993), and the following Internet sites: (1) http://telemedicine.org/Botanica/Bot5.htm and (2) http://www.ars-grin.gov/cgi-bin/duke/chemical_activity.pl.

Flors and Nonell (2006) have described phototoxic phytoalexins (phytoalexins are toxins that are induced and not present in unstressed plants) having a phenalenone group (Fig. 21.4) in their molecular structure. They produce singlet oxygen upon irradiation with UV-A to blue light and are toxic to fungi. They were first found in Haemodoraceae and Musaceae (Cooke and Edwards 1981), but subsequently found to be common not only in members of these families but also in Strelitziaceae. They were so long overlooked because they do not occur in unstressed plants. Related substances are present also in species of Annonaceae, Lauraceae, Magnoliaceae, Fumariaceae, Menispermaceae, and Papaveraceae (Flors and Nonell 2006).

21.3 Phototoxins of Fungal Plant Parasites

Phototoxins are not used only for plant defense but also for attack on plants by parasitic fungi. So far only one case has been thoroughly researched, but a number of plant pathogenic fungi produce photosensitizing substances. A review of the subject (Daub and Ehrenshaft 2000) has recently appeared.

The best known example of a plant parasite using a phototoxin to weaken its host is the genus *Cercospora*. About 500 parasitic *Cercospora* species are known and cause, for example, leaf spot of sugar beet, gray leaf spot of corn, purple seed stain of soybean, frogeye leaf spot of tobacco, and brown eye spot of coffee. For sugar beet the active pigment, cercosporin (Fig. 21.5), has been isolated from 34 *Cercospora* species grown in culture, while other species do not produce cercosporin and still can parasitize plants.

Cercosporin is a type II phototoxin. After reaching its triplet state during illumination, it reacts with oxygen to form singlet oxygen. The singlet oxygen destroys the cell membrane of host cells, which leads to leakage of nutrients to the fungus.

Of course, the fungus has cell membranes which could be damaged by cercosporin, so it must have some defense against its own toxin. In culture, they can accumulate up to millimolar toxin in the medium without observable toxic effects. In fact, it defends itself in two ways:

1. As long as the cercosporin is inside the hyphae, it is kept in a reduced form, which in light produces only a small amount of singlet oxygen. After secretion to the environment, it is oxidized to the highly active form. The two forms can be easily distinguished under the microscope, since the reduced form has a green fluorescence and the oxidized one a red fluorescence.
2. In addition, the fungus is extraordinarily well equipped with a set of triplet and singlet oxygen quenchers. That they are efficient is shown by the fact that *Cercospora* is resistant also to the effects of other singlet oxygen–producing phototoxins. Among the quenchers of singlet oxygen pyridoxine is thought to be particularly important for *Cercospora*.

Interestingly, *Cercospora* does not produce cercosporin in darkness (when it would be of no use); its synthesis is triggered by light.

Pigments having structures related to cercosporin (perylenequinones, see Fig. 25.1), and presumably having a corresponding function, are produced by a number of other fungi: by *Cladosporium* species, by the bamboo pathogens *Shiraia bambusicola* and *Hypocrella bambusae*, and by *Stemphylium botryosum* and some *Alternaria* and *Elsinoe* species. Also, light-requiring fungal toxins of other types are known, produced by *Cercospora* species and *Dothistroma pini* (Jalal et al. 1992; Stoessl et al. 1990).

21.4 Phototoxic Drugs and Cosmetics

Many phototoxic drugs are either antibiotics or medications for blood pressure and heart disease, but there are also others. In combination with light, they may cause extreme sunburn, vesicles, hives, and edema. Among antibiotics, photosensitivity reactions have more commonly been noted after administration of the following: doxycycline ("Vibramycin," etc.), demeclocycline, tetracycline (Fig. 21.6), nalidixic acid, and lomefloxacin. For blood pressure and heart medications, a similar short list includes

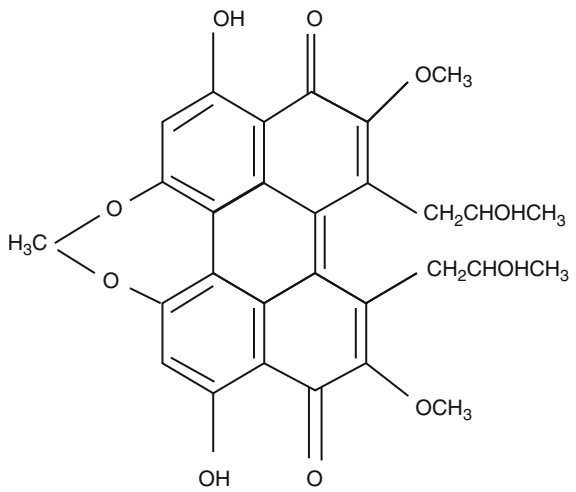

Fig. 21.5 Cercosporin, the phototoxin of the parasitic fungus *Cercospora*

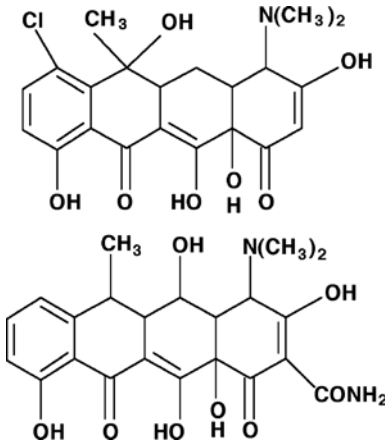

Fig. 21.6 (*Top*) Chlortetracycline, the first tetracycline, introduced in 1948. Tetracycline itself (introduced in 1952) has the same structure, with hydrogen in place of chlorine. (*Bottom*) Doxycycline, introduced in 1968, is one of the most potent photosensitizers among the tetracyclines

hydrochlorothiazide (occurs as an ingredient in a large number of formulations), chlorothiazide, furosemide, and amiodarone. Amiodarone is responsible for an unusually high number of cases. Among other drugs causing photosensitivity reactions, chlorpromazine and other phenothiazines and birth control pills containing estrogens may be mentioned.

Somewhat surprising is the fact that also sun lotions containing para-aminobenzoic acid (PABA) or esters of it, which are sold to protect from the sun, are also a common cause of photosensitivity. These substances were selected for their ability to absorb UV-B radiation (daylight with wavelength below 315 nm), since formerly this radiation was supposed to be the only threat from sunlight. At the long-wavelength edge of their absorption band, they let radiation through to depths where they can cause the photosensitivity reactions.

It is well known that use of perfumes in combination with sunlight is unwise, because many perfumes are phototoxic or at least discolor the skin when exposed to sunlight. This is, of course, because many, if not most of them, are based on plant extracts and often contain substances mentioned in the section on phototoxins in plant defense. Freund (1916) described skin discolorations, which he attributed to eau de cologne containing bergamot oil, although he did not clearly understand the role of sunlight. Bergamot orange, *Citrus bergamia*, like many other *Citrus* species, was later found to contain photosensitizing substances.

21.5 Metabolic Disturbances Leading to Phototoxic Effects of Porphyrins or Related Compounds

A number of different disturbances in both humans and animals lead to the appearance in the skin of phototoxic compounds such as uro- and coproporphyrinogens (porphyrin precursors), protoporphyrin IX (the immediate precursor of heme, Fig. 21.7), and phylloerythrin (a breakdown product of chlorophyll, Fig. 21.8). These substances are phototoxins of type II, generating singlet oxygen in light.

In human patients, a variety of diseases have been described which go under the common designation of porphyria. With the exception of a type called acute intermittent porphyria, they lead to photosensitivity of the skin: variegate porphyria (Frank and Christiano 1998) and hereditary coproporphyria (acute porphyrias with increased levels of both porphyrin precursors and porphyrins) and porphyria cutanea tarda, erythropoietic protoporphyria, and congenital porphyria (nonacute porphyrias with increased levels of porphyrins). Porphyria is due to a disturbance in either the liver (hepatic porphyria or protoporphyria) or the red blood cells

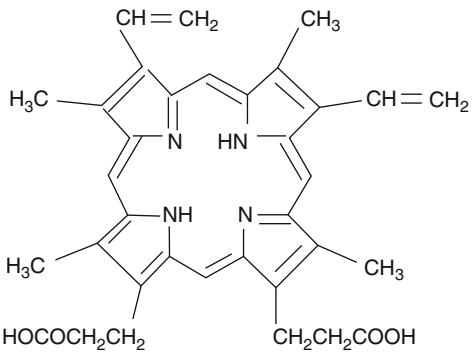

Fig. 21.7 Protoporphyrin IX, the immediate precursor of heme, which accumulates in protoporphyria due to lack of ferrochelatase (or inhibition of the enzyme due to, e.g., lead poisoning)

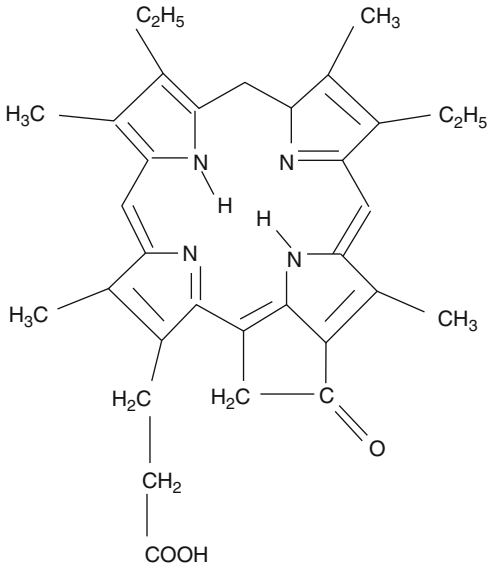

Fig. 21.8 Phylloerythrin, which causes phototoxicity in animals due to malfunctioning of the liver. In healthy animals, the substance is broken down in the liver

(erythropoietic porphyria or protoporphyria). To complicate things further, an erythrohepatic porphyria has recently been described (Gauer et al. 1995), and erythropoietic porphyria may lead to secondary damage to the liver.

Porphyria may be inherited or acquired, and even in cases when it is caused by environment, lifestyle, alcohol (Doss et al. 1999), lead poisoning, liver transplantation (Sheth et al. 1994), etc., inherited predisposition may play a role. Gross et al. (2000) remark in a review: "The molecular genetics of the porphyrias is very heterogenous. Nearly every family has its own mutation." Correct treatment of porphyria is therefore not easy and requires very careful examination. Porphyria cannot be cured, but symptoms can often be ameliorated in other ways than avoidance of light. There are prospects for a future cure of the erythropoietic

protoporphyria. In this condition, the enzyme ferrochelatase is lacking in the red blood cells, causing accumulation of protoporphyrin IX. It may become possible to cure this by retroviral-mediated gene transfer to the bone marrow (Todd 1994). At present the symptoms can be alleviated using β-carotene, interestingly the same compound as used by plants to quench triplet chlorophyll.

In ruminants, another group of diseases with names such as geeldikkop ("yellow head") and alveld is important. Geeldikkop, affecting sheep in South Africa, is the best studied of these. It is caused by saponins in the plant *Tribulus terrestris* (puncture vine or calthrops of the family Zygophyllaceae) grazed upon by sheep (Miles et al. 1994; Wilkins et al. 1996). Liver damage caused by these saponins prevents breakdown of phylloerythrin, a substance produced from chlorophyll by acid in the stomach and rumen bacteria. The phylloerythrin is circulated to skin capillaries, where it can be exposed to light. In other parts of the world, *Panicum* species such as kleingrass or bambatsi grass, *P. coloratum* (Muchiri et al. 1980; Bridges et al. 1987; Regnault 1990), and switchgrass, *P. virgatum* (Puoli et al. 1992), cause the same disease in sheep and in horses (Cornick et al. 1988).

Similar symptoms were induced by *Myoporum laetum* in calves (Raposo et al. 1998), and buttercup (*Ranunculus bulbosus*) has been suspected as a cause in cattle (Kelch et al. 1992). Mold fungi in hay and fungi in pasture can cause similar problems (Scruggs et al. 1994; Casteel et al. 1995). Finally, it has been known for a long time that cyanobacterial toxins in drinking water can cause liver damage with associated photosensitivity in cattle. In the case of the fungus *Pithomyces chartarum* in lamb pasture (Hansen et al. 1994), it is not clear whether the photosensitivity is due to primary photosensitization or liver damage.

21.6 Polycyclic Aromatic Hydrocarbons as Phototoxic Contaminants in Aquatic Environments

21.6.1 Nature and Occurrence of PAHs

Some compounds have a potential to become toxic or acquire increased toxicity when they interact with natural or simulated sunlight. Such compounds with a possible environmental relevance include photoactive insecticides, such as naturally occurring α-terthienyl (Kagan et al. 1984, 1987) and some photodynamic dyes (Larson and Berenbaum 1988); a carbamate insecticide (Zaga et al. 1998), trinitrotoluene (TNT, an explosive), and some related compounds (Davenport et al. 1994); photoreactive nanomaterials (e.g., TiO_2 nanoparticles) used in a wide range of products (Ma et al. 2012); and many polycyclic aromatic hydrocarbons (PAHs) (Newsted and Giesy 1987; Arfsten et al. 1996; Diamond 2003). PAHs, composed of multiple aromatic rings (Fig. 21.9) and present in coal and petroleum products, are widespread organic environmental contaminants, some having carcinogenic potential. PAHs can be introduced into the environment, for example, through incomplete combustion of organic matter. In aquatic environments oil spills, surface runoff from land, and industrial and domestic wastewaters are among the possible sources of PAH contamination, as well as airborne PAHs entering aquatic systems through dry fallout and rainfall (Neff 1979, 1985; Latimer and Zheng 2003). Photoenhanced toxicity of petroleum products (Pelletier et al. 1997; Wernersson 2003) and creosote (Schirmer et al. 1999) has been related to phototoxicity of PAHs present. Furthermore, liquid-phase elutriates of petroleum-containing sediments (Davenport and Spacie 1991), urban stormwater runoff (Ireland et al. 1996), as well as PAH-contaminated sediments (Ankley et al. 1994; Monson et al. 1995) contain phototoxic components, suggesting the role of PAHs. Interaction with solar radiation has also been shown to increase the toxicity of weathered oil (Cleveland et al. 2000; Little et al. 2000; Barron et al. 2003).

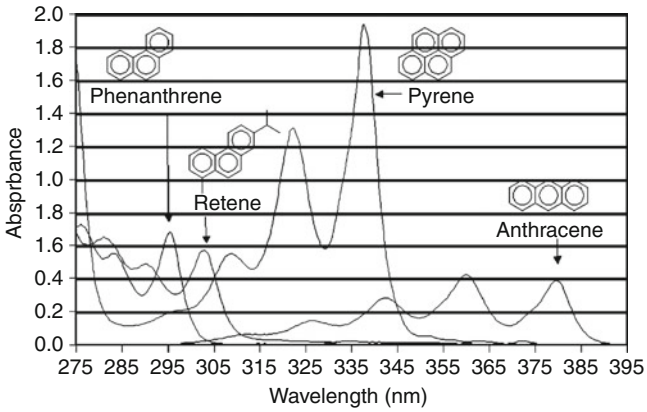

Fig. 21.9 Absorption spectra of anthracene, pyrene, phenanthrene, and retene (7-isopropyl-1-methylphenanthrene) (10 mg^{-1} in dimethyl sulfoxide) (Modified from Huovinen et al. (2001), with permission from Elsevier Science)

Although generally considered relatively acutely non-toxic under normal laboratory lighting, numerous PAHs, such as anthracene, benzo[a]pyrene (3,4-benzopyrene, benzo[d,e,f]chrysene), fluoranthene, and pyrene, have a potential to become highly toxic in the presence of UV radiation, and a risk that PAHs constitute through this photoenhanced toxicity to aquatic organisms has been recognized (reviewed by Landrum et al. 1987; Arfsten et al. 1996; Ankley et al. 2003; Diamond 2003; Pelletier et al. 2006). Since bioassays used to test the toxicity of chemicals are commonly carried out in the laboratory under artificial lighting not including UV radiation, the risk related to photoactive compounds in natural conditions can be underestimated with traditional toxicity testing. On the other hand, the

ecological relevance of PAH phototoxicity evaluations and their use in risk assessment has been criticized (McDonald and Chapman 2002) as often experimental approaches cannot be considered representative of natural environmental conditions where a suite of factors interact.

21.6.2 Mechanisms of PAH Phototoxicity

Because of their chemical structure, many PAHs absorb energy in the UV waveband (Newsted and Giesy 1987; Huang et al. 1993; Diamond et al. 2000; Huovinen et al. 2001) (Fig. 21.9). According to the quantitative structure/activity relationship (QSAR) model, the phototoxicity of PAHs can be related to the HOMO-LUMO gap (i.e., energy difference between the highest occupied molecular orbital and the lowest unoccupied molecular orbital), which has been suggested as a suitable ground state index of the electronic structure relating to absorbed energy and molecular stability (Mekenyan et al. 1994). However, the comparison of the phototoxic potency of PAHs is complicated because it is also related to the bioaccumulation potential of each compound (Boese et al. 1998). Contaminated environments generally contain a mixture of numerous PAHs, and phototoxicity of PAH mixtures has been regarded as somewhat additive (Swartz et al. 1997; Boese et al. 1999; Erickson et al. 1999). Co-exposure with other contaminants, for example, methyl tertiary-butyl ether or piperonyl butoxide, has been shown to increase bioconcentration and photoinduced toxicity of some PAHs (Cho et al. 2003; Weinstein and Garner 2008). Also, substituted PAHs can contribute to phototoxicity (Boese et al. 1998; Kosian et al. 1998). With some exceptions, phototoxicity is likely in a substituted PAH only if the aromatic structure of its parent compound is phototoxic (Veith et al. 1995).

Phototoxicity of PAHs is reported to occur mainly via photosensitization and/or photomodification reactions. The role of PAHs as active photosensitizers is related to their capability of forming triplet states and transferring their triplet energy to oxygen, potentially resulting in the formation of biologically damaging singlet oxygen (Foote 1987; Larson and Berenbaum 1988; see Chap. 1). Photosensitization reactions of bioaccumulated PAHs in biological matrices are regarded as important mechanisms for phototoxicity, which is supported by studies demonstrating enhanced toxicity when bioaccumulation of PAHs in aquatic organisms is followed by exposure to UV radiation in clean uncontaminated water (Bowling et al. 1983; Allred and Giesy 1985; Ankley et al. 1994, 1997; Boese et al. 1997; Monson et al. 1999; Huovinen et al. 2001). Phototoxicity via photosensitization is considered a function of both PAH dose in tissue and UV intensity (Ankley et al. 1995; Huovinen et al. 2001).

In addition to photodegradation (Neff 1979, 1985), PAHs may be photomodified into more toxic forms, for example, via photooxidation (McConkey et al. 1997; Mallakin et al. 1999; Lampi et al. 2006). Photomodification of PAH can result in a complex mixture of products (Mallakin et al. 1999). The enhanced toxicity of many photoproducts can probably be attributed to increased aqueous solubility and thus potentially increased bioavailability, as well as increased bioactivity (Duxbury et al. 1997; McConkey et al. 1997). Although many photomodified PAHs are toxic as such, they can be phototoxic as well (Huang et al. 1993; Mallakin et al. 1999). According to model predictions, photosensitization and photomodification contribute additively to phototoxicity (Huang et al. 1997; Krylov et al. 1997; Mezey et al. 1998; El-Alawi et al. 2002).

21.6.3 Factors Affecting Exposure to Phototoxicity of PAHs in Aquatic Systems

Due to their hydrophobic nature, PAHs tend to accumulate in sediments and organic particles (Neff 1979, 1985), resulting in a decrease in their bioavailability to organisms. However, disturbance of contaminated sediment, for example, during a storm or dredging, may result in mobilization and resuspension of PAHs in the water, increasing the risk of phototoxicity (Davenport and Spacie 1991; Ireland et al. 1996). On the other hand, because of their lipophilic nature, PAHs also tend to bioaccumulate in organisms. In addition to waterborne PAHs, possible routes of exposure to PAHs are their bioaccumulation from contaminated sediments (Ankley et al. 1994; Boese et al. 1998), through maternal transfer (Hall and Oris 1991; Pelletier et al. 2000), via ingested food and potentially also via the food chain. Factors related to PAH bioavailability and bioaccumulation, defining finally the body burden (together with metabolism) (reviewed by Burgess et al. 2003), form the basis for the photosensitization-based phototoxicity risk.

The potential for UV exposure varies in different types of waters. UV-B penetration depths can range from a few centimeters in highly humic lakes (Lean 1998; Huovinen et al. 2003; Kirk 2011), few meters in costal marine waters (Huovinen and Gómez 2011), to dozens of meters in clear oceanic waters (Smith et al. 1992; Kirk 2011). The spectra of underwater UV irradiance change with depth, as penetration decreases with decreasing wavelength (Lean 1998; Huovinen et al. 2003; Kirk 2011). This spectral variation among natural waters affect the potential for phototoxicity (Barron et al. 2000), since the phototoxic response is related to the UV absorption characteristics of a compound (Newsted and Giesy 1987; Diamond et al. 2000; Huovinen et al. 2001; Lampi et al. 2006) (Fig. 21.9). Aquatic biota in PAH-contaminated areas (particularly in clear, shallow waters and littoral areas, which often provide habitats for various aquatic

organisms during reproduction and early development) may be at risk. UV exposure and thus phototoxicity can also be increased, for example, during low flow (Ireland et al. 1996) or when organisms move up in the water column. Other factors, such as increased turbidity, which reduce the penetration of UV radiation in the water column, can attenuate phototoxicity as well (Ireland et al. 1996).

In addition to strongly contributing to attenuation of UV radiation, humic substances have a complex role in aquatic systems in potentially affecting the phototoxicity of PAHs. Dissolved humic material may mitigate the potential for photoinduced toxicity (Gensemer et al. 1998, 1999) by reducing the bioaccumulation of PAHs to organisms (Oris et al. 1990; Weinstein and Oris 1999). On the other hand, the risk for phototoxicity may be increased as a result of higher UV penetration in aquatic ecosystems due to decrease of dissolved organic carbon content induced by UV radiation (Morris and Hargreaves 1997), acidification, and climate warming (Schindler et al. 1996). Humic substances as potential photosensitizers (Larson and Berenbaum 1988) play a role in photodegradation of aquatic contaminants via formation of reactive oxygen species by UV radiation (Boule et al. 1999).

In all, a variety of factors affecting the exposure of organisms to PAHs and to UV radiation, as well as interactions between multiple environmental factors and stressors present in natural conditions, complicate the risk assessment for phototoxicity. Currently ecotoxicological risk assessment is facing new challenges under global climate change scenarios, also influencing photoactivated toxicity as both PAH and UV exposure can potentially be altered by climate change in several ways (Gouin et al. 2013; Hooper et al. 2013).

21.6.4 Phototoxicity of PAHs to Aquatic Biota

Since the early evidence of a potential risk of co-exposure to PAHs and UV radiation to aquatic organisms and environments (e.g., Bowling et al. 1983; Oris and Giesy 1985), information on the mechanisms of phototoxicity and the effects on aquatic biota have been increasing over the last decades. Phototoxicity of PAHs has been demonstrated in a variety of aquatic organisms, including bacteria, phytoplankton, aquatic macrophytes, zooplankton, benthic invertebrates, insect larvae, amphibians, bivalves, and fish, with responses in biota ranging from acute lethality to chronic effects, such as reproductive impairment (reviewed by Landrum et al. 1987; Arfsten et al. 1996; Ankley et al. 2003; Diamond 2003; Pelletier et al. 2006; Barron 2007).

Species vary in their sensitivity to the phototoxicity of PAHs (Boese et. al. 1997; Hatch and Burton 1998; Spehar et al. 1999), which could be related to behavioral (Hatch and Burton 1999) and potentially to metabolic and morphological differences. Translucent early life stages are expected to be more vulnerable to phototoxicity than pigmented juvenile and adult stages (Barron et al. 2005). Also previous exposure of organisms to UV radiation can lead to development of protective mechanisms (e.g., pigmentation) reducing their sensitivity (Boese et al. 1997; Gevertz et al. 2012). Defense mechanisms against oxidative stress, for example, carotenoid pigments, could mitigate the effects of PAH phototoxicity by quenching singlet oxygen generated from PAH photosensitization (Gala and Giesy 1993). Xanthophyll cycling, which has traditionally been associated with photochemical reactions to excess solar radiation, has been suggested also as an energy dissipative response to photoinduced PAH toxicity in microalgae (Southerland and Lewitus 2004). Photoprotective UV-absorbing compounds, such as mycosporine-like amino acids reported in various aquatic organisms or phenolic compounds (phlorotannins) of brown algae, might affect phototoxic potential by providing protection against UV exposure and possibly via their antioxidant activity (Dunlap and Yamamoto 1995; Huovinen et al. 2010). Furthermore, a possibility for repair of phototoxic effects has been demonstrated (Oris and Giesy 1986).

Although phototoxicity potential of numerous PAHs is well known, attention should be paid to the ecological relevance of especially laboratory-based results when using them in risk evaluations (McDonald and Chapman 2002). Overall, the importance of incorporating phototoxicity in water and sediment quality evaluations has been recognized, and recently conceptual frameworks (the adverse outcome pathway) have been proposed to improve predictive approaches and support ecotoxicological risk assessment (Ankley et al. 2010).

References

Allred PM, Giesy JP (1985) Solar radiation-induced toxicity of anthracene to *Daphnia pulex*. Environ Toxicol Chem 4:219–226

Ankley GT, Collyard SA, Monson PD, Kosian PA (1994) Influence of ultraviolet light on the toxicity of sediments contaminated with polycyclic aromatic hydrocarbons. Environ Toxicol Chem 13:1791–1796

Ankley GT, Erickson RJ, Phipps GL, Mattson VR, Kosian PA, Sheedy BR, Cox JS (1995) Effects of light intensity on the phototoxicity of fluoranthene to a benthic macroinvertebrate. Environ Sci Technol 29:2828–2833

Ankley GT, Erickson RJ, Sheedy BR, Kosian PA, Mattson VR, Cox JS (1997) Evaluation of models for predicting the phototoxic potency of polycyclic aromatic hydrocarbons. Aquat Toxicol 37:37–50

Ankley GT, Burkhard LP, Cook PM, Diamond SA, Erickson RJ, Mount DR (2003) Assessing risks from photoactivated toxicity of PAHs to aquatic organisms. In: Douben PET (ed) PAHs: an ecotoxicological perspective. Wiley, Chichester, pp 275–296

Ankley GT, Bennett RS, Erickson RJ, Hoff DJ, Hornung MW, Johnson RD, Mount DR, Nichols JW, Russom CL, Schmieder PK, Serrano JA, Tietge JE, Villenueve DL (2010) Adverse outcome pathways: a conceptual framework to support ecotoxicology research and risk assessment. Environ Toxicol Chem 29:730–741

Arfsten DP, Schaeffer DJ, Mulveny DC (1996) The effects of near ultraviolet radiation on the toxic effects of polycyclic aromatic hydrocarbons in animals and plants: a review. Ecotoxicol Environ Saf 33:1–24

Barron MG (2007) Sediment-associated phototoxicity to aquatic organisms. Hum Ecol Risk Assess 13:317–321

Barron MG, Little EE, Calfee R, Diamond S (2000) Quantifying solar spectral irradiance in aquatic habitats for the assessment of photoenhanced toxicity. Environ Toxicol Chem 19:920–925

Barron MG, Carls MG, Short JW, Rice SD (2003) Photoenhanced toxicity of aqueous phase and chemically dispersed weathered Alaska North Slope crude oil to Pacific herring eggs and larvae. Environ Toxicol Chem 22:650–660

Barron MC, Carls MG, Short JW, Rice SD, Heintz RA, Rau M, DiGiulio R (2005) Assessment of the phototoxicity of weathered Alaska North Slope crude oil to juvenile pink salmon. Chemosphere 60: 105–110

Boese BL, Lamberson JO, Swartz RC, Ozretich RJ (1997) Photoinduced toxicity of fluoranthene to seven marine benthic crustaceans. Arch Environ Contam Toxicol 32:389–393

Boese BL, Lamberson JO, Swartz RC, Ozretich R, Cole F (1998) Photoinduced toxicity of PAHs and alkylated PAHs to a marine infaunal amphipod (*Rhepoxynius abronius*). Arch Environ Contam Toxicol 34:235–240

Boese BL, Ozretich RJ, Lamberson JO, Swartz RC, Cole FA, Pelletier J, Jones J (1999) Toxicity and phototoxicity of mixtures of highly lipophilic PAH compounds in marine sediment: can the ∑PAH model be extrapolated? Arch Environ Contam Toxicol 36:270–280

Boule P, Bolte M, Richard C (1999) Phototransformations induced in aquatic media by NO_3^-/NO_2^-, Fe^{III} and humic substances. In: Boule P (ed) The handbook of environmental chemistry, vol 2, Part I. Environmental photochemistry. Springer, Berlin, pp 181–215

Bowling JW, Leversee GJ, Landrum PF, Giesy JP (1983) Acute mortality of anthracene-contaminated fish exposed to sunlight. Aquat Toxicol 3:79–90

Bridges DH, Camp BJ, Liningston CW, Bailey EM (1987) Kleingrass (*Panicum coloratum* L.) poisoning in sheep. Vet Pathol 24:525–531

Burgess RM, Ahrens MJ, Hickey CW, den Besten PJ, ten Hulscher D, van Hattum B, Meador JP, Douben PET (2003) An overview of the partitioning and bioavailability of PAHs in sediments and soils. In: Douben PET (ed) PAHs: an ecotoxicological perspective. Wiley, Chichester, pp 99–126

Casteel SW, Rottinghaus GE, Hohson GC, Wicklow DT (1995) Liver disease in cattle induced by consumption of moldy hay. Vet Hum Toxicol 37:248–251

Cho EA, Bailer AJ, Oris JT (2003) Effect of methyl tert-butyl ether on the bioconcentration and photoinduced toxicity of fluoranthene in fathead minnow larvae (*Pimephales promelas*). Environ Sci Technol 37:1306–1310

Cleveland L, Little EE, Calfee RD, Barron MG (2000) Photoenhanced toxicity of weathered oil to *Mysidopsis bahia*. Aquat Toxicol 49:63–76

Cornick JL, Carter GK, Bridges CH (1988) Kleingrass-associated hepatoxicosis in horses. J Am Vet Med Assoc 193:932–935

Cooke RG, Edwards JM (1981) Naturally occuring phenalenones and related compounds. In Cadby PA et al. (eds) Progress in the chemistry of organic natural products, Springer-Verlag, Vienna, pp. 153–190

Daub ME, Ehrenshaft M (2000) The photoactivated *Cercospora* toxin cercosporin: contributions to plant disease and fundamental biology. Annu Rev Phytopathol 38:461–490

Davenport R, Spacie A (1991) Acute phototoxicity of harbor and tributary sediments from lower Lake Michigan. J G Lakes Res 17: 51–56

Davenport R, Johnson LR, Schaeffer DJ, Balbach H (1994) Phototoxicology. 1. Light-enhanced toxicity of TNT and some related compounds to *Daphnia magna* and *Lytechinus variegatus* embryos. Ecotoxicol Environ Saf 27:14–22

Delaey E, Vandenbougaerde A, Merlevede W, de Witte P (2000) Photocytotoxicity of hypericin in nomroxic and hypoxic conditions. J Photochem Photobiol B: Biol 56:19–24

Diamond SA (2003) Photoactivated toxicity in aquatic environments. In: Helbling EW, Zagarese H (eds) UV effects in aquatic organisms and ecosystems. The Royal Society of Chemistry, Cambridge, pp 219–250

Diamond SA, Mount DR, Burkhard LP, Ankley GT, Makynen EA, Leonard EN (2000) Effect of irradiance spectra on the photoinduced toxicity of three polycyclic aromatic hydrocarbons. Environ Toxicol Chem 19:1389–1396

Doss MO, Kuhnel A, Gross U, Sieg I (1999) Hepatic porphyrias and alcohol. Med Klin 94:314–328

Downmum KR (1992) Light-activated plant defence. New Phytol 122:401–420

Dunlap WC, Yamamoto Y (1995) Small-molecule antioxidants in marine organisms: antioxidant activity of mycosporine-glycine. Comp Biochem Physiol 112B:105–114

Duxbury CL, Dixon DG, Greenberg BM (1997) Effects of simulated solar radiation on the bioaccumulation of polycyclic aromatic hydrocarbons by the duckweed *Lemna gibba*. Environ Toxicol Chem 16:1739–1748

Ehrenshaft M, Roberts JE, Mason RP (2013) Hypericin-mediated photooxidative damage of α-crystallin in human lens epithelial cells. Free Radic Biol Med 60:347–354

El-Alawi YS, Huang X-D, Dixon DG, Greenberg BM (2002) Quantitative structure-activity relationship for the photoinduced toxicity of polycyclic aromatic hydrocarbons to the luminescent bacteria *Vibrio fischeri*. Environ Toxicol Chem 21:2225–2232

Erickson RJ, Ankley GT, DeFoe DL, Kosian PA, Makynen EA (1999) Additive toxicity of binary mixtures of phototoxic polycyclic aromatic hydrocarbons to the oligochaete *Lumbriculus variegatus*. Toxicol Appl Pharmacol 154:97–105

Flors C, Nonell S (2006) Light and singlet oxygen in plant defense against pathogens: phototoxic phenalenone phytoalexins. Acc Chem Res 39:293–300

Foote, CS (1987) Type I and type II mechanisms of photodynamic action. In: Heitz JR, Downum KR (eds) Light-activated pesticides. ACS Symposium Series 339. American Chemical Society, Washington, DC, pp 22–38

Frank J, Christiano AM (1998) Variegate porphyria: past, present and future. Skin Pharmacol Appl Skin Physiol 11:310–320

Freund E (1916) Über bisher noch nicht beschriebene kunstliche Hautverfarbungen. Dermatol Wochenschr 63:931–933

Gala WR, Giesy JP (1993) Using the carotenoid biosynthesis inhibiting herbicide, fluridone, to investigate the ability of carotenoid pigments to protect algae from the photoinduced toxicity of anthracene. Aquat Toxicol 27:61–70

Gauer EB, Doss MO, Riemann JF (1995) Erythrohepatic protoporphyria, a rare cause in the differential-diagnosis of parenchymatous jaundice. Deut Med Wochenschr 120:713–717

Gensemer RW, Dixon DG, Greenberg BM (1998) Amelioration of the photo-induced toxicity of polycyclic aromatic hydrocarbons by a commercial humic acid. Ecotoxicol Environ Saf 39:57–64

Gensemer RW, Dixon DG, Greenberg BM (1999) Using chlorophyll *a* fluorescence to detect the onset of anthracene photoinduced toxicity in *Lemna gibba*, and the mitigating effects of a commercial humic acid. Limnol Oceanogr 44:878–888

Gevertz AK, Tucker AJ, Bowling AM, Williamson GE, Oris JT (2012) Differential tolerance of native and nonnative fish exposed to ultraviolet radiation and fluoranthene in Lake Tahoe (California/ Nevada), USA. Env Toxicol Chem 31:1129–1135

Gouin T, Armitage JM, Cousins IT, Muir DCG, Ng CA, Reid L, Tao S (2013) Influence of global climate change on chemical fate and

bioaccumulation: the role of multimedia models. Environ Toxicol Chem 32:20–31

Gross U, Hoffmann GF, Doss MO (2000) Erythropoi9etic and hepatic porphyrias. J Inherit Metab Dis 23:641–661

Hall AT, Oris JT (1991) Anthracene reduces reproductive potential and is maternally transferred during long-term exposure in fathead minnows. Aquat Toxicol 19:249–264

Hansen DE, McCoy RD, Hedstrom OR, Snyder SP, Ballerstedt PB (1994) Photosensitization associated with exposure to *Pithomyces chartarum* in lambs. J Vet Med Assoc 204:1668–1671

Hatch AC, Burton GA Jr (1998) Effects of photoinduced toxicity of fluoranthene on amphibian embryos and larvae. Environ Toxicol Chem 17:1777–1785

Hatch AC, Burton GA Jr (1999) Photo-induced toxicity of PAHs to *Hyalella azteca* and *Chironomus tentans*: effects of mixtures and behavior. Environ Pollut 106:157–167

Hooper MJ, Ankley GT Cristol DA, Maryoung LA, Noyes PD, Pinkerton, KE (2013) Interactions between chemical and climate stressors: a role for mechanistic toxicology in assessing climate change risks. Env Toxicol Chem 32:32–48

Huang X-D, Dixon DG, Greenberg BM (1993) Impacts of UV radiation and photomodification on the toxicity of PAHs to the higher plant *Lemna gibba* (duckweed). Environ Toxicol Chem 12:1067–1077

Huang X-D, Krylov SN, Ren L, McConkey BJ, Dixon DG, Greenberg BM (1997) Mechanistic quantitative structure-activity relationship model for the photoinduced toxicity of polycyclic aromatic hydrocarbons. II. An empirical model for the toxicity of 16 polycyclic aromatic hydrocarbons to the duckweed *Lemna gibba* L. G-3. Environ Toxicol Chem 16:2296–2303

Huovinen P, Leal P, Gómez I (2010) Interacating effects of copper, nitrogen and ultraviolet radiation on the physiology of three south Pacific kelps. Mar Freshw Res 61:330–341

Huovinen P, Gómez I (2011) Spectral attenuation of solar radiation in Patagonian fjord and coastal waters and implications for algal photobiology. Cont Shelf Res 31:254–259

Huovinen PS, Soimasuo MR, Oikari AOJ (2001) Photoinduced toxicity of retene to *Daphnia magna* under enhanced UV-B radiation. Chemosphere 45:683–691

Huovinen PS, Penttilä H, Soimasuo MR (2003) Spectral attenuation of solar ultraviolet radiation in humic lakes in Central Finland. Chemosphere 51:205–214

Ireland DS, Burton GA Jr, Hess GG (1996) *In situ* toxicity evaluations of turbidity and photoinduction of polycyclic aromatic hydrocarbons. Environ Toxicol Chem 15:574–581

Jalal MAF, Hossain MB, Robeson DI, van der Helm D (1992) *Cercospora beticola* phytotoxins: cebetins that are photoactive, Mg^{2+}-binding, chlorinated anthraquinone-xanthone conjugates. J Am Chem Soc 114:5967–5971

Kagan J, Kagan PA, Buhse HE Jr (1984) Light-dependent toxicity of α-terthienyl and anthracene toward late embryonic stages of *Rana pipiens*. J Chem Ecol 10:1115–1122

Kagan J, Bennett WJ, Kagan ED, Maas JL, Sweeney SA, Kagan IA, Seigneurie E, Bindokas V (1987) α-Terthienyl as a photoactive insecticide: toxic effects on nontarget organisms. In: Heitz JR, Downum KR (eds) Light-activated pesticides. ACS Symposium Series 339. American Chemical Society, Washington, DC, pp 176–191

Kelch WR, Kerr IA, Adair HS, Boyd GD (1992) Suspected buttercup (*Ranunculus bulbosus*) toxicosis with secondary photosensitization in Charolais heifer. Vet Hum Toxicol 34:238–239

Kirk JTO (2011) Light and photosynthesis in aquatic ecosystems, 3rd edn. Cambridge University Press, Cambridge

Kosian PA, Makynen EA, Monson PD, Mount DR, Spacie A, Mekenyan OG, Ankley GT (1998) Application of toxicity-based fractionation techniques and structure-activity relationship models for the identification of phototoxic polycyclic aromatic hydrocarbons in sediment pore water. Environ Toxicol Chem 17:1021–1033

Krylov SN, Huang X-D, Zeiler LF, Dixon DG, Greenberg BM (1997) Mechanistic quantitative structure-activity relationship model for the photoinduced toxicity of polycyclic aromatic hydrocarbons: I. Physical model based on chemical kinetics in a two-compartment system. Environ Toxicol Chem 16:2283–2295

Lampi MA, Gurska J, McDonald KIC, Xie F, Huang X-D, Dixon DG, Greenberg BM (2006) Photoinduced toxicity of polycyclic aromatic hydrocarbons to *Daphnia magna*: Ultraviolet-mediated effects and the toxicity of polycyclic aromatic hydrocarbon photoproducts. Environ Toxicol Chem 25:1079–1087

Landrum PF, Giesy JP, Oris JT, Allred PM (1987) Photoinduced toxicity of polycyclic aromatic hydrocarbons to aquatic organisms. In: Vandermeulen JH, Hrudey SE (eds) Oil in freshwater: chemistry, biology, countermeasure technology. Proc. Symp. Oil Pollution in Freshwater, Edmonton, Alberta, Canada. Pergamon Press, New York, pp 304–318

Larson RA, Berenbaum MR (1988) Environmental phototoxicity. Solar ultraviolet radiation affects the toxicity of natural and man-made chemicals. Environ Sci Technol 22:354–360

Latimer JS, Zheng J (2003) The sources, transport, and fate of PAHs in the marine environment. In: Douben PET (ed) PAHs: an ecotoxicological perspective. Wiley, Chichester, pp 9–33

Lean D (1998) Attenuation of solar radiation in humic waters. In: Hessen DO, Tranvik LJ (eds) Aquatic humic substances. Ecology and biogeochemistry, vol 133, Ecol. Studies. Springer, Berlin, pp 109–124

Little EE, Cleveland L, Calfee R, Barron MG (2000) Assessment of the photoenhanced toxicity of a weathered oil to the tidewater silverside. Environ Toxicol Chem 19:926–932

Lovell CR (1993) Plants and the skin. Blackwell Scientific Publishing, Oxford

Ma H, Brennan A, Diamond SA (2012) Phototoxicity of TiO_2 nanoparticles under solar radiation to two aquatic species: *Daphnia magna* and Japanese medaka. Environ Toxicol Chem 31:1621–1629

Mallakin A, McConkey BJ, Miao G, McKibben B, Snieckus V, Dickson DG, Greenberg BM (1999) Impacts of structural photomodification on the toxicity of environmental contaminants: anthracene photooxidation products. Ecotoxicol Environ Saf 43:204–212

McConkey BJ, Duxbury CL, Dixon DG, Greenberg BM (1997) Toxicity of a PAH photooxidation product to the bacteria *Photobacterium phosphoreum* and the duckweed *Lemna gibba*: effects of phenanthrene and its primary photoproduct, phenanthrenequinone. Environ Toxicol Chem 16:892–899

McDonald BG, Chapman PM (2002) PAH phototoxicity—an ecologically irrelevant phenomenon? Mar Pollut Bull 44:1321–1326

Mekenyan OG, Ankley GT, Veith GD, Call DJ (1994) QSARs for photoinduced toxicity: I. Acute lethality of polycyclic aromatic hydrocarbons to Daphnia magna. Chemosphere 28:567–582

Mezey PG, Zimpel Z, Warburton P, Walker PD, Irvine DG, Huang X-D, Dixon DG, Greenberg BM (1998) Use of quantitative shape-activity relationships to model the photoinduced toxicity of polycyclic aromatic hydrocarbons: electron density shape features accurately predict toxicity. Environ Toxicol Chem 17:1207–1215

Miles CO, Wilkins AL, Erasmus GL, Kellerman TS, Coetzer J (1994) Photosensitivity in South Africa. 7. Chemical composition of biliary crystals from a sheep with experimentally induced geeldikkop. Onderstepoort J Vet Res 61:215–222

Monson PD, Ankley GT, Kosian PA (1995) Phototoxic response of *Lumbriculus variegatus* to sediments contaminated by polycyclic aromatic hydrocarbons. Environ Toxicol Chem 14:891–894

Monson PD, Call DJ, Cox DA, Liber K, Ankley GT (1999) Photoinduced toxicity of fluoranthene to northern leopard frogs (*Rana pipiens*). Environ Toxicol Chem 18:308–312

Morris DP, Hargreaves BR (1997) The role of photochemical degradation of dissolved organic carbon in regulating the UV transparency of three lakes on the Pocono Plateau. Limnol Oceanogr 42: 239–249

Muchiri DJ, Bridges CH, Ueckert DN, Bailey EM (1980) Photosensitization of sheep on kleingrass pasture. J Am Vet Sci Assoc 177:353–354

Neff JM (1979) Polycyclic aromatic hydrocarbons in the aquatic environment. Sources, fates and biological effects. Applied Science Publishers Ltd, London

Neff JM (1985) Polycyclic aromatic hydrocarbons. In: Rand GM, Petrocelli SR (eds) Fundamentals of aquatic toxicology. Methods and applications. Hemisphere Publishing Corporation, New York, pp 416–454

Newsted JL, Giesy JP (1987) Predictive models for photoinduced acute toxicity of polycyclic aromatic hydrocarbons to *Daphnia magna*, Strauss (Cladocera, Crustacea). Environ Toxicol Chem 6:445–461

Oris JT, Giesy JP Jr (1985) The photoenhanced toxicity of anthracene to juvenile sunfish (*Lepomis* spp.). Aquat Toxicol 6:133–146

Oris JT, Giesy JP Jr (1986) Photoinduced toxicity of anthracene to juvenile bluegill sunfish (*Lepomis macrochirus* Rafinesque): photoperiod effects and predictive hazard evaluation. Environ Toxicol Chem 5:761–768

Oris JT, Hall AT, Tylka JD (1990) Humic acids reduce the photoinduced toxicity of anthracene to fish and daphnia. Environ Toxicol Chem 9:575–583

Pathak MA (1986) Phytodermatitis. Clin Dermatol 4:102–121

Pathak MA, Fitzpatrick TB (1992) The evolution of photochemotherapy with psoralens and UVA (PUVA): 2000 BC to 1992 AD. J Photochem Photobiol B: Biol 14:3–22

Pelletier MC, Burgess RM, Ho KT, Kuhn A, McKinney RA, Ryba SA (1997) Phototoxicity of individual polycyclic aromatic hydrocarbons and petroleum to marine invertebrate larvae and juveniles. Environ Toxicol Chem 16:2190–2199

Pelletier MC, Burgess RM, Cantwell MG, Serbst JR, Ho KT, Ryba SA (2000) Importance of maternal transfer of the photoreactive polycyclic aromatic hydrocarbon fluoranthene from benthic adult bivalves to their pelagic larvae. Environ Toxicol Chem 19:2691–2698

Pelletier E, Sargian P, Demers S (2006) Ecotoxicological effects of combined UVB and organic contaminants in coastal waters: a review. Photochem Photobiol 82:981–993

Puoli JR, Reid RI, Belesky DP (1992) Photosensitization in lambs grazing switchgrass. Agron J 84:1077–1080

Raposo JB, Mendez MC, de Adrade BB, Riet-Correa F (1998) Experimental intoxication by *Myoporum kaetyn* in cattle. Vet Hum Toxicol 40:275–277

Regnault TRH (1990) Secondary photosensitization of sheep grazing bambatsi grass (Panicum coloratum var. makarikariense). Aust Vet J 67:419

Samadi A, Martinez LA, Miranda MA, Morera IM (2001) Mechanism of lipid peroxidation photosensitized by tiaprofenic acid: Product studies using linoleic acid and 1,4-cyclohexadienes as model substrates. Photochem Photobiol 73:359–365

Schindler, DW, Curtis PJ, Parker B, Stainton MP (1996) Consequences of climate warming and lake acidification for UV-B penetration in North American boreal lakes. Nature 379:705–708

Schirmer K, Herbrick J-AS, Greenberg BM, Dixon DG, Bols NC (1999) Use of fish gill cells in culture to evaluate the cytotoxicity and photocytotoxicity of intact and photomodified creosote. Environ Toxicol Chem 18:1277–1288

Scruggs DW, Blue GK (1994) Toxic hepatopathy and photosensitization in cattle fed moldy alfalfa hay. J Am Vet Med Assoc 204:264–266

Sheth AP, Esterly NB, Rabinowitz IG, Poh-Fitzpatrick MB (1994) Cutaneous porphyria-like photosensitivity after liver transplantation. Arch Dermatol 130:614–617

Smith RC, Prézelin BB, Baker KS, Bidigare RR, Boucher NP, Coley T, Karentz D, MacIntyre S, Matlick HA, Menzies D, Ondrusek M, Wan Z, Waters KJ (1992) Ozone depletion: ultraviolet radiation and phytoplankton biology in Antarctic waters. Science 255: 952–959

Southerland HA, Lewitus AJ (2004) Physiological responses of estuarine phytoplankton to ultraviolet light-induced fluoranthene toxicity. J Exp Mar Biol Ecol 298:303–322

Spehar RL, Poucher S, Brooke LT, Hansen DJ, Champlin D, Cox DA (1999) Comparative toxicity of fluoranthene to freshwater and saltwater species under fluorescent and ultraviolet light. Arch Environ Contam Toxicol 37:496–502

Stoessl A, Abramowski Z, Lester HH, Rock GL, Towers GHN (1990) Further toxic properties of the fungal metabolite dothistromin. Mycopathologia 112:179–186

Swartz RC, Ferraro SP, Lamberson JO, Cole FA, Ozretich RJ, Boese BL, Schults DW, Behrenfeld M, Ankley GT (1997) Photoactivation and toxicity of mixtures of polycyclic aromatic hydrocarbon compounds in marine sediment. Environ Toxicol Chem 16:2151–2157

Todd DJ (1994) Erythropoietic protoporphyria. Br J Dermatol 131: 751–766

Veith GD, Mekenyan OG, Ankley GT, Call DJ (1995) A QSAR analysis of substituent effects on the photoinduced acute toxicity of PAHs. Chemosphere 30:2129–2142

Weinstein JE, Oris JT (1999) Humic acids reduce the bioaccumulation and photoinduced toxicity of fluoranthene to fish. Environ Toxicol Chem 18:2087–2094

Weinstein JE, Garner TR (2008) Piperonyl butoxide enhances the bioconcentration and photoinduced toxicity of fluoranthene and benzo[a]pyrene to larvae of the grass shrimp (Palaemonetes pugio). Aquat Toxicol 87:28–36

Wernersson A-S (2003) Predicting petroleum phototoxicity. Ecotoxicol Environ Saf 54:355–365

Wilkins AL, Miles CO, DeKock WT, Erasmus GL, Basson AT, Kellerman TS (1996) Photosensitivity in South Africa. 9. Structure elucidation of a α-glucosidase-treated saponin from *Tribulus terrestris*, and the identification of saponin chemotypes of South African *T. terrestris*. Onderstepoort J Vet Res 63:327–334

Zaga A, Little EE, Rabeni CF, Ellersieck MR (1998) Photoenhanced toxicity of a carbamate insecticide to early life stage anuran amphibians. Environ Toxicol Chem 17:2543–2553