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**Reviews of
Environmental
Contamination
and Toxicology**

**With Cumulative and Comprehensive
Index of Subjects Covered
Volumes 201-210**

David M. Whitacre
Editor

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Foreword

International concern in scientific, industrial, and governmental communities over traces of xenobiotics in foods and in both abiotic and biotic environments has justified the present triumvirate of specialized publications in this field: comprehensive reviews, rapidly published research papers and progress reports, and archival documentations. These three international publications are integrated and scheduled to provide the coherency essential for nonduplicative and current progress in a field as dynamic and complex as environmental contamination and toxicology. This series is reserved exclusively for the diversified literature on "toxic" chemicals in our food, our feeds, our homes, recreational and working surroundings, our domestic animals, our wildlife, and ourselves. Tremendous efforts worldwide have been mobilized to evaluate the nature, presence, magnitude, fate, and toxicology of the chemicals loosed upon the Earth. Among the sequelae of this broad new emphasis is an undeniable need for an articulated set of authoritative publications, where one can find the latest important world literature produced by these emerging areas of science together with documentation of pertinent ancillary legislation.

Research directors and legislative or administrative advisers do not have the time to scan the escalating number of technical publications that may contain articles important to current responsibility. Rather, these individuals need the background provided by detailed reviews and the assurance that the latest information is made available to them, all with minimal literature searching. Similarly, the scientist assigned or attracted to a new problem is required to glean all literature pertinent to the task, to publish new developments or important new experimental details quickly, to inform others of findings that might alter their own efforts, and eventually to publish all his/her supporting data and conclusions for archival purposes.

In the fields of environmental contamination and toxicology, the sum of these concerns and responsibilities is decisively addressed by the uniform, encompassing, and timely publication format of the Springer triumvirate:

Reviews of Environmental Contamination and Toxicology [Vol. 1 through 97 (1962–1986) as Residue Reviews] for detailed review articles concerned with any aspects of chemical contaminants, including pesticides, in the total environment with toxicological considerations and consequences.

Bulletin of Environmental Contamination and Toxicology (Vol. 1 in 1966) for rapid publication of short reports of significant advances and discoveries in the fields of air, soil, water, and food contamination and pollution as well as methodology and other disciplines concerned with the introduction, presence, and effects of toxicants in the total environment.

Archives of Environmental Contamination and Toxicology (Vol. 1 in 1973) for important complete articles emphasizing and describing original experimental or theoretical research work pertaining to the scientific aspects of chemical contaminants in the environment.

Manuscripts for Reviews and the Archives are in identical formats and are peer reviewed by scientists in the field for adequacy and value; manuscripts for the *Bulletin* are also reviewed, but are published by photo-offset from camera-ready copy to provide the latest results with minimum delay. The individual editors of these three publications comprise the joint Coordinating Board of Editors with referral within the board of manuscripts submitted to one publication but deemed by major emphasis or length more suitable for one of the others.

Coordinating Board of Editors

Preface

The role of *Reviews* is to publish detailed scientific review articles on all aspects of environmental contamination and associated toxicological consequences. Such articles facilitate the often complex task of accessing and interpreting cogent scientific data within the confines of one or more closely related research fields.

In the nearly 50 years since *Reviews of Environmental Contamination and Toxicology* (formerly *Residue Reviews*) was first published, the number, scope, and complexity of environmental pollution incidents have grown unabated. During this entire period, the emphasis has been on publishing articles that address the presence and toxicity of environmental contaminants. New research is published each year on a myriad of environmental pollution issues facing people worldwide. This fact, and the routine discovery and reporting of new environmental contamination cases, creates an increasingly important function for *Reviews*.

The staggering volume of scientific literature demands remedy by which data can be synthesized and made available to readers in an abridged form. *Reviews* addresses this need and provides detailed reviews worldwide to key scientists and science or policy administrators, whether employed by government, universities, or the private sector.

There is a panoply of environmental issues and concerns on which many scientists have focused their research in past years. The scope of this list is quite broad, encompassing environmental events globally that affect marine and terrestrial ecosystems; biotic and abiotic environments; impacts on plants, humans, and wildlife; and pollutants, both chemical and radioactive; as well as the ravages of environmental disease in virtually all environmental media (soil, water, air). New or enhanced safety and environmental concerns have emerged in the last decade to be added to incidents covered by the media, studied by scientists, and addressed by governmental and private institutions. Among these are events so striking that they are creating a paradigm shift. Two in particular are at the center of ever-increasing media as well as scientific attention: bioterrorism and global warming. Unfortunately, these very worrisome issues are now superimposed on the already extensive list of ongoing environmental challenges.

The ultimate role of publishing scientific research is to enhance understanding of the environment in ways that allow the public to be better informed. The term “informed public” as used by Thomas Jefferson in the age of enlightenment

conveyed the thought of soundness and good judgment. In the modern sense, being “well informed” has the narrower meaning of having access to sufficient information. Because the public still gets most of its information on science and technology from TV news and reports, the role for scientists as interpreters and brokers of scientific information to the public will grow rather than diminish. Environmentalism is the newest global political force, resulting in the emergence of multinational consortia to control pollution and the evolution of the environmental ethic. Will the new politics of the twenty-first century involve a consortium of technologists and environmentalists, or a progressive confrontation? These matters are of genuine concern to governmental agencies and legislative bodies around the world.

For those who make the decisions about how our planet is managed, there is an ongoing need for continual surveillance and intelligent controls to avoid endangering the environment, public health, and wildlife. Ensuring safety-in-use of the many chemicals involved in our highly industrialized culture is a dynamic challenge, for the old, established materials are continually being displaced by newly developed molecules more acceptable to federal and state regulatory agencies, public health officials, and environmentalists.

Reviews publishes synoptic articles designed to treat the presence, fate, and, if possible, the safety of xenobiotics in any segment of the environment. These reviews can be either general or specific, but properly lie in the domains of analytical chemistry and its methodology, biochemistry, human and animal medicine, legislation, pharmacology, physiology, toxicology, and regulation. Certain affairs in food technology concerned specifically with pesticide and other food-additive problems may also be appropriate.

Because manuscripts are published in the order in which they are received in final form, it may seem that some important aspects have been neglected at times. However, these apparent omissions are recognized, and pertinent manuscripts are likely in preparation or planned. The field is so very large and the interests in it are so varied that the editor and the editorial board earnestly solicit authors and suggestions of underrepresented topics to make this international book series yet more useful and worthwhile.

Justification for the preparation of any review for this book series is that it deals with some aspect of the many real problems arising from the presence of foreign chemicals in our surroundings. Thus, manuscripts may encompass case studies from any country. Food additives, including pesticides, or their metabolites that may persist into human food and animal feeds are within this scope. Additionally, chemical contamination in any manner of air, water, soil, or plant or animal life is within these objectives and their purview.

Manuscripts are often contributed by invitation. However, nominations for new topics or topics in areas that are rapidly advancing are welcome. Preliminary communication with the editor is recommended before volunteered review manuscripts are submitted.

Summerfield, North Carolina

David M. Whitacre

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Attenuation of Chromium Toxicity by Bioremediation Technology

Monalisa Mohanty and Hemanta Kumar Patra

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1 Introduction

Human activities, such as industrial and energy production, mineral excavation, and transportation, result in contamination by polluting substances, many of which are dangerous. Chromium (Cr) is one of the most toxic heavy metals and is discharged into the environment through various human activities. Extensive use of chromium in electroplating, tanning, and textile dyeing and as a biocide in power plant cooling

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water results in the discharge of chromium-containing effluents. The pace of release of organic pollutants, and Cr in particular, into the environment is growing exponentially and is enhancing concerns that such releases pose potentially serious risks to human health. Heavy metals, such as chromium, are not destroyed by degradation and are therefore accumulating in the environment.

Chromium has received special attention because it is known to be toxic to humans and animals (WHO 1988; ATSDR 2001) and to plants as well (Panda and Patra 1997; Zayed and Terry 2003; Panda and Choudhury 2005; Shanker et al. 2005a; Nayak et al. 2008; Mohanty and Patra 2009). The World Health Organization (WHO 1988) has addressed the toxic threats of chromium (Cr^{+6}) and has listed it as a human carcinogen (ATSDR 2001).

The Cr that contaminates soils, groundwater, and surface waters must physically be removed from many contaminated sites if these sites are to be rendered usable. The traditional solution for dealing with Cr-polluted sites is to shift contaminated soil into landfills. Such a method may be effective, but is expensive and involves exposure risks of its own. An alternative for rendering Cr-contaminated sites suitable for sustainable development may involve use of living organisms. This would typically include plants or microbes that are capable of degrading, absorbing, or otherwise removing toxic materials from the environment; treatment with such organisms would be designed to stabilize tailings (mined ore) and Cr contaminants in situ. Such approaches are called bioremediation, and are not only feasible, but less costly and more environmental friendly than the traditionally used approaches. In most cases, bioremediation relies for its effectiveness on natural processes within the selected organism. The purpose of the present review is to provide insights into how the risks posed by chromium-contaminated sites may be attenuated at different places worldwide, by applying the various tools and techniques of bioremediation.

2 Chemistry of Chromium

Chromium was discovered by N.L. Vauquelin in 1798. This substance is a steel-gray, lustrous, hard, and brittle metal that belongs to Group VIB, the transition series elements. It is the seventh most abundant element on earth and is the 21st most abundant element in crustal rocks (Katz and Salem 1994). Cr exhibits a range of oxidation states (Table 1). Of the many oxidation states possible for chromium, there are two stable forms, i.e., Cr(III) and Cr(VI). The most toxic form of Cr is Cr(VI). The primary physico-chemical properties of chromium are summarized in Table 2. Within the normal ranges of Eh and pH in soil, chromium exists in four states, viz., two trivalent forms (Cr^{+3} and CrO_2^{2-}) and two hexavalent forms ($\text{Cr}_2\text{O}_7^{-2}$ and CrO_4^{-2}) (Bartlett and Kimble 1976). At a pH above 4, the solubility of chromium(III) decreases and apparent complete precipitation occurs at pH 5.5 (Bartlett and Kimble 1976). In aqueous systems, chromium exists primarily in two oxidation states, viz., hexavalent chromium (Cr-VI) and trivalent chromium (Cr-III) (Table 3A). Of these, Cr(III) is generally considered to be the more stable

Table 1 Oxidation states of various chemical species of chromium

Chemical species of chromium	Oxidation states	Examples/occurrence	Remarks
Elemental	0	—	Does not occur naturally
Divalent	Cr(II)	CrBr ₂ , CrCl ₂ , CrFe ₂ , CrSe, Cr ₂ Si	Unstable and oxidized to Cr(III) stage
Trivalent	Cr(III)	CrB, CrB ₂ , CrBr ₃ , CrCl ₃ .6H ₂ O	Occur in nature as ores such as ferrochromite
Tetravalent	Cr(IV)	CrCl ₃ , CrF ₃ , CrN, KCr(SO ₄) ₂ .12 H ₂ O	Does not occur naturally
Pentavalent	Cr(V)	CrO ₂ , CrF ₄	Does not occur naturally
Hexavalent	Cr(VI)	(NH ₄) ₂ CrO ₄ , BaCrO ₄ , CaCrO ₄ , K ₂ CrO ₄ , 2Cr ₂ O ₇	Rarely occur in nature, most toxic form, produced by human activities

Sources: Nieboer and Jusys (1988) and Katz and Salem (1994)

Table 2 Physico-chemical properties of chromium

Properties	Analytical data
Phase at room temperature	Solid
Color	Silvery white
Atomic number	24
Atomic mass	51.996 g/mol
Electronic configuration	[Ar]4s ¹ 3d ⁵
Electronegativity	1.66
Density	7.19 g/cm ³ at 20°C
Hardness	9 Mohs
Melting point	1,875°C or 2,130.2 K
Boiling point	2,672°C or 2,963 K
van der Waals radius	0.127 nm
Ionic radius	0.061 nm (+3); 0.044 nm (+6)
Isotopes	6
Energy of first ionization	651.1 kJ/mol
Heat of fusion	15.3 kJ/mol
Heat of vaporization	347 kJ/mol
Heat of atomization	397 kJ/mol
Thermal conductivity	93.9 J/m s K
Electrical conductivity (1mohm/cm)	77.519
Electron affinity	64.3 kJ/mol
Atomic radius	128 pm
Common oxidation numbers	+3, +6, -2, -1
Other oxidation numbers	+1, +2, +4, +5
Standard potential	-0.71 V (Cr ³⁺ /Cr)

form (Banu and Ramaswamy 1997). Cr(VI) is not only more toxic than Cr(III), the latter form of the element is also an essential trace element connected with the glucose tolerance factor (Mertz 1969; Saner 1980). The concentration of chromium found in various environmental media (soil, water, air, and living organisms), and its recommended limits in such media and organisms are presented in Table 3B.

Table 3 Concentration of chromium found in the environment and recommended limits in environmental media and in organisms**A** Concentration limits in organisms and environmental media

Sample types	Concentrations ($\mu\text{g/L}$)		References
	Cr(VI)	Cr(III)	
Fresh water life	1	8	Krishnamurthy and Wilkens (1994), Pawlisz (1997)
Marine life	1	50	Krishnamurthy and Wilkens (1994), Pawlisz (1997)
Irrigation water	8	5	Krishnamurthy and Wilkens (1994), Pawlisz (1997)
Drinking water	50	50	Krishnamurthy and Wilkens (1994), Pawlisz (1997)

B Concentrations of chromium found in various environmental media

Sample types	Total 'Cr' concentrations	References
Natural soil	5–1,000 mg/kg 30–300 mg/kg	Adriano (1986) Katz and Salem (1994)
Fresh water	0–117 $\mu\text{g/L}$ Avg-9.7 $\mu\text{g/L}$	Pawlisz (1997) Pawlisz (1997)
Seawater	0–0.5 $\mu\text{g/L}$	Pawlisz (1997)
Air	1–5,45,000 ngm ³ 100 ngm ³	Pawlisz (1997) U.S. EPA (1983)
Plants	0.006–18 mg/kg	Pawlisz (1997)
Animals	0.03–1.6 mg/kg	Pawlisz (1997)

3 Sources of Chromium in the Environment

3.1 Production, Sources, and Uses of Chromium

The level of world production of chromium is in the order of 10^7 t/year. In 1998, the production level stood at 3.4 million t. The countries that constitute the major sources of chromite ore, from which Cr is taken, and their proportionate share (%) are as follows: South Africa (36%), USSR (28%), Turkey (7%), India (6.5%), Albania (6%), Finland (5%), Zimbabwe (5%), and trace amounts in other countries. In India, approximately 98% of chromium deposits are located in the state of Orissa, of which 94% fall in the Sukinda mining belt of Jajpur district and the rest (4%) in the Dhenkanal, Balasore, and Keonjhar districts.

Cr is used in stainless steel alloys, which consume between 50 and 70% of total Cr demand. Cr is also used in the chemical industry for leather tanning, pigment production, and electroplating (Stern 1982). Chandra et al. (1997) estimated that, in India alone, 2,000–3,200 t of elemental Cr escape into the environment annually from tanning industry emissions. The ferrochrome industries emit 12,360 t Cr/year. The combustion of fossil fuels, such as coal (Kessler et al. 1971) and petroleum, also

results in the release of chromium into the atmosphere. Coal combustion releases 520 t Cr/year. Moreover, chromium is widely distributed in rocks, fresh water, and seawater, and these may serve as natural sources of Cr loss to the environment. Limestone contains traces of Cr of up to 300 mg Cr/kg limestone (McGrath and Smith 1990).

Chromium metal is used mainly for making steel and other alloys (ATSDR 1998). Cr provides additional strength, hardness, and toughness to steel. It also gives corrosion resistance to steel. Stainless steel, high-speed steel, and corrosion and heat-resistant steel are important varieties of chromium steel. Low-Cr steels (less Cr and small amounts of Ni) are used in the rails of railroads, automobiles, cutlery, and cooking utensils. Cr steel includes stainless steels (12–18% Cr) and super stainless steels (12–30% Cr and 7–10% Ni). The former are used to make cutlery and cooking utensils, and the latter are used to make parts for aircraft and high-speed trains. Chromium compounds, either in chromium(III) or chromium(VI) forms, are also used for chrome plating, manufacture of dyes and pigments, leather and wood preservation, and the treatment of cooling tower water. Smaller amounts are used in drilling mud, textiles, and toner for copying machines (ATSDR 1998). Chromite is used in refractory industry (commercial entities that use heat-resistant materials to line the walls of high-temperature furnaces and reactors) due to its corrosion- and high temperature-resistance and its chemically neutral character. The chromite ore, after extraction (ore tailings), is used in the form of lumps, bricks, or cement in linings, especially linings used in steel blast furnaces. Chromite is used to make chromates and dichromates of Na, K, and Cr and pigments such as chromic oxide green and chromic acid. In turn, these pigments are used in Cr-plating solutions.

3.2 Chromium in Fertilizers, Animal Wastes, and Sewage Sludge

Fertilizers and animal wastes contain chromium (McGrath and Smith 1990). The chromium content of sewage sludge ranges from 40 to 8,000 ppm (Berrow and Webber 1972). Fly ash from thermal plants that consume coal is often disposed of by distributing it on land, and this constitutes another major source of Cr input to soils. Other sources, which contribute Cr in trace amounts to the environment, are asbestos, brake linings in vehicles, and aerosols produced from Cr catalysts used in emission-reduction systems for treating exhaust fumes.

4 Chromium Transport and Accumulation in Plants

Chromium is similar to other heavy metals (e.g., As, Cd, Co, Cu, Ni, Sn, and Zn) in that it is phytotoxic at a concentration above a certain threshold level (Nieboer and Richardson 1980). Cr as a trace element is not ranked as an ‘essential element’ for plants (Huffman and Allaway 1973). However, its essentiality for animal nutrition has received considerable attention from those who study the role of plants as Cr transmitters in the food chain.

Chromium is actively transported across biological membranes in both prokaryotes (Dreyfuss 1964) and eukaryotes (Wiegand et al. 1985; Alexander and Ashet 1995). Once taken inside the cell, Cr(VI) is reduced to Cr(III), possibly because of the unstable nature of chromium in intermediate states like Cr(V) and Cr(IV) (Arslan et al. 1987; Liu et al. 1995). Evidently, Cr^{+3} and CrO_4^{-2} enter vascular tissue with difficulty, but once they gain entry, they are readily transported to the xylem. Hexavalent chromium in the form of CrO_4^{-2} moves more readily than does Cr^{+3} , because the latter may be detained by ion exchange interactions on vessel walls (Skeffington et al. 1976).

CrO_4^{-2} is actively transported across membranes with the help of sulfate-containing protein carriers and, in roots, is immediately converted to Cr^{+3} , possibly by an Fe(III) reductase enzyme (Zayed et al. 1998). In contrast, Cr^{+3} is passively absorbed and retained by cation exchange sites on cell walls (Marschner 1995). McGrath (1982) reported that despite the different properties of Cr^{+3} and CrO_4^{-2} , there were no substantial differences in their rates of absorption and uptake. Skeffington et al. (1976) have suggested that Cr(III) uptake does not require metabolic energy (is a passive transport process, i.e., diffusion), whereas the uptake of Cr(VI) ions occurs by active transport mechanisms. Translocation studies in vegetable crops with Cr indicated that CrO_4^{-2} is converted in roots to Cr^{+3} by all plants tested (Zayed et al. 1998), and translocation of Cr from roots to shoots was extremely limited.

Sulfate (SO_4^{-2}) and other Cr(VI) anions are competitive inhibitors of chromate and inhibit its uptake. In contrast, the presence of Ca^{+3} stimulates the uptake of chromate (Shewry and Peterson 1974). Many researchers (Huffman and Allaway 1973; Lahouti and Peterson 1979; Myttenaere and Mousny 1974; Parr and Taylor 1980; McGrath 1982; Zayed et al. 1998) were of the opinion that Cr(III) and Cr(VI) are poorly translocated to the aerial parts (shoots) of plants and tend to be largely retained at sites in the root. Chromium is absorbed by the roots from nutrient solution as Cr^{+3} or CrO_4^{-2} . It has been found that roots accumulate 10–100 times more Cr than do shoots (Zayed et al. 1998; Srivastava et al. 1999; Skeffington et al. 1976).

Transport and accumulation of chromium depends on the formation of complexes that act to enhance Cr uptake and availability in plants (Athalye et al. 1995; Shanker et al. 2005a, b; Torresdey et al. 2005; Zhuang et al. 2007). Complexes are formed with several organic compounds, i.e., oxalic acids, malate, glycine, EDTA (ethylene diamine tetraacetic acid), DTPA (diethylene triamine pentaacetic acid), EDDHA (ethylene diamine di-ortho hydroxy phenylacetic acid), etc. When complexed with different compounds, uptake rates of Cr^{+3} and Cr^{+6} varied (Athalye et al. 1995; Shanker et al. 2005a; Zhuang et al. 2007). Metabolic inhibitors such as sodium azide and dinitrophenol (DNP) substantially reduced uptake of Cr^{+6} . Alternatively, Cr^{+3} uptake was not affected by metabolic inhibitors in barley seedlings (Skeffington et al. 1976). In several plants (tomato, wheat, potato, bean, pea, beet, barley, maize, spinach, etc.), Cr uptake was enhanced when supplied as Cr(III), Cr(VI), Cr-oxalate, Cr-tartarate, Cr-EDTA, Cr-DTPA, Cr-methionine, or Cr-citrate (Cary et al. 1977a; Athalye et al. 1995; Erenoglu et al. 2007). Salicylic acid complexed with chromium substantially increased the uptake of Cr (Tripathi and Chandra 1991). This may

result from the fact that Cr-EDTA, Cr-DTPA, or other complexed chromium compounds are not retained or impeded by ion exchange interactions with the cell walls (Myttenaere and Mousny 1974; Athalye et al. 1995; Cary et al. 1977a).

Translocation and accumulation of chromium depends on the following major factors: the oxidation state of chromium (Mishra et al. 1995) and the concentration of chromium in the growth medium (Kleiman and Cogliatti 1998) or concentration in the plant (Zayed et al. 1998). The experimental results also indicated that Cr accumulation was comparatively higher in plants supplied with CrO_4^{2-} and Cr^{+6} than in plants supplied with Cr^{+3} . The high concentrations of Cr in the nutrient medium also led to an increased accumulation of Cr in plants (Zayed et al. 1998; Mishra et al. 1995). Vegetable crops, *Brassica* spp., sulfur-loving species (cauliflower, cabbage, and kale), spices, and many other crops have the ability to accumulate more Cr in roots than in other plant parts. Water hyacinth is known as a hyperaccumulator of Cr (Lytle et al. 1998; Zhu et al. 1999).

5 Chromium Toxicity

The biological effects of Cr toxicity have been studied and reviewed by many workers (Zayed et al. 1998; Zayed and Terry 2003; Skeffington et al. 1976; Srivastava et al. 1999; Zhu et al. 1999; McGrath 1982; McGrath et al. 1997; Panda and Patra 1997, 2004; Nayak et al. 2004; Erenoglu et al. 2007). Chromium contamination is known to affect organisms in the biosphere at many locations worldwide (Cunningham et al. 1997; Raskin and Ensley 2000; Meagher 2000). Excess concentrations of several heavy metals, including Cr(VI), have resulted in the disruption of both natural aquatic and terrestrial ecosystems (Gardea Torresdey et al. 1998; Meagher 2000). The increase of Cr levels in soil and water has been reported to cause adverse effects to microflora and growing plants. These adverse effects are addressed below.

5.1 Effects of Chromium on Microorganisms

The toxic and mutagenic effects of chromates on microbes are also well documented. The toxic effects of Cr on bacteria and algae have been reviewed by Wong and Trevors (1988). Mertz (1969) reported that chromium is a component of the electron transport chain located inside the plasma membrane of prokaryotes. Cr(VI) acts as a terminal electron acceptor as does oxygen. Ross et al. (1981) found that 10–12 mg/L of Cr(VI) was inhibitory to soil bacteria in liquid media, whereas Cr(III) at this concentration had no effect. Ajmal et al. (1984) reported that chrome-electroplating waste was toxic to saprophytic and nitrifying bacteria, and showed increasing toxicity as the Cr(VI) content of the waste increased. *Rhizobium* has also been observed to be very sensitive to Cr (Misra et al. 1994, 2004; Thatoi 1994; Patnaik 1995; Mishra 2002).

The in vivo generation of Cr(V) from Cr(VI) by *Spirogyra* and *Mougeotia* has been reported by Liu et al. (1995). Growth of *Scenedesmus acutus* was detected at concentrations of Cr exceeding 15 ppm (Travieso et al. 1999). However, Brady et al. (1994) reported that colonial algal growth of *Scenedesmus* and *Selenastrum* was possible at levels of 100 ppm of Cr(III), but not at 100 ppm of Cr(VI). A lengthening in the lag growth phase was induced by Cr(VI), whereas the growth rate was decreased by Cr(III), in *Euglena gracilis* (Brochiero et al. 1984). Cr(VI) also induced an alteration in the cytoskeleton, which may have resulted in the loss of motility (Bassi and Donini 1984). Inhibition of photosynthesis by Cr has also been reported in *Chlorella* (Wong and Trevors 1988) and in *Scenedesmus* (Corradi et al. 1995). In estuarine algae, Cr(VI) toxicity is inversely proportional to salinity (Frey et al. 1983).

In *Saccharomyces cerevisiae*, chromium toxicity was stronger in cells grown in non-fermentable substrates (Henderson 1989). Other effects included inhibition of oxygen uptake (Henderson 1989) and induction of *petite* mutations. These results suggest that chromate specifically targets the mitochondria of *S. cerevisiae* (Henderson 1989). Additional effects of Cr in *S. cerevisiae* include gene conversion (Kharab and Singh 1985; Galli et al. 1985) and induction of mutations (Kharab and Singh 1985; Galli et al. 1985; Cheng et al. 1998).

5.2 Effects of Chromium on Human Health

Chromium pollution is known to induce respiratory and skin diseases and affect mucous membranes (ATSDR 1998; USEPA 1998; WHO 1988). Skin ulcers that do not heal are caused by chromium exposure. Such respiratory and skin diseases were frequently found in workers at chromite mining and processing sites. The Cr exposure also affects individuals in the nearby villages. Gastrointestinal and neurological effects have been noted after inhalation exposure to high concentrations of chromium(VI). Dermal exposure to Cr(VI) also induces skin burns in humans (ATSDR 1998; USEPA 1998; WHO 1988). Chronic inhalation exposure to chromium(VI) in humans results in respiratory tract effects, such as perforations and ulcerations of the septum, bronchitis, decreased pulmonary function, pneumonia, asthma, nasal itching, and soreness (ATSDR 1998; USEPA 1998; WHO 1988). Workers exposed to chromium(VI) compounds may be at risk for developing cancer. Based on results of animal studies, EPA has concluded that only chromium(VI) should be classified as a human carcinogen (ATSDR 1998; USEPA 1999).

There is only limited information available on the reproductive effects of chromium(VI) in humans exposed by the inhalation route; this information suggests that exposure to chromium(VI) may result in complications during pregnancy and childbirth (ATSDR 1998). Chromium(III) is an essential element in humans and has a recommended daily intake of 50–200 µg/day for adults (ATSDR 1998). Acute oral animal tests have shown chromium(III) to have moderate toxicity (ATSDR 1998; USDHHS 1993).

5.3 Chromium Phytotoxicity

Chromium is mainly present in the environment in two stable forms i.e., Cr(III) and Cr(VI). The activities of these two forms markedly differ because of their different abilities to cross biological membranes (Debatto and Luciani 1988). Chromium(VI), as chromate, readily penetrates plant cuticle and membranes via a general anion transport system, whereas Cr(III) complexes do not diffuse through plant membranes. The accumulation of chromium(III) at the cell surface results from cation binding activity.

Several workers have reported chromium toxicity in plants (Koenig 1910; Lyon et al. 1970; Wallace et al. 1976; Watanabe 1984; Moral et al. 1993; Misra et al. 1994, 2004). Such toxic effects of chromium includes stunted growth, chlorosis, reduced crop yield, delayed germination, senescence and premature falling of leaves, biochemical lesions, reduced enzyme activity, and reduced synthesis of proteins, amino acids, and enzymes such as RNase, invertase, amylase, catalase, peroxidase, and Fe-reductase. The phytotoxic effects of chromium were first reported a century ago by Koenig (1911). Other effects from uptake of chromium by plants include reduced rates of growth, damage to cell walls and membranes, and changes to plant metabolic status (Williamson and Johnson 1981; Panda and Patra 1997; Nayak et al. 2004; Mohanty et al. 2005). The visual symptoms of Cr toxicity in plants include stunted growth, poorly developed root system, and curled and discolored leaves (Hunter and Vergnano 1953; Misra et al. 1994, 2004). Corradi and Bianchi (1993) also reported suppression of lateral roots as a symptom of chromium toxicity. However, Gaw and Soong (1942) saw reduction in the dry weight and nodulation of peas after adding chromic sulfate to the soil in which they grew. Chlorotic bands on cereals were noted by several researchers (Kabata-Pendias and Pendias 1992; Panda and Patra 1997, 2004; Patra et al. 2002; Nayak et al. 2004), and the exposures that produced such effects resulted in yield reduction (Parr and Taylor 1982; Misra et al. 1994). Immediate wilting and plant death have also been reported from exposure to very high levels of Cr (Parr and Taylor 1982). It has been reported (Austenfeld 1979; Bassi et al. 1990; Bonet et al. 1991; Choudhury and Panda 2005; Mohanty et al. 2005, 2008, 2009; Nayak et al. 2008) that high concentrations of Cr in plants (rice, wheat, lentil, green gram, pistia, lemna, moss, and beans) resulted in stunted growth, reduced chlorophyll content, higher activity of certain enzymes, and higher bioaccumulation of Cr in roots.

5.3.1 Inhibition of Germination and Seedling Growth

High levels of chromium may inhibit seed germination and subsequent seedling growth. Cr(VI) concentrations above 2 mM can affect pea seed germination and suppress the growth of radicle and plumule (Bishnoi et al. 1993). Chromium toxicity causing inhibition of seed germination and radicle growth in plants was also observed by others (Atta Aly et al. 1999; Corradi and Bianchi 1993; Liu et al. 1993; Nayari et al. 1997; Panda et al. 2002). The germination and growth of bush bean were substantially affected at 500 mg/kg by Cr in soil (Parr 1982). Chromium

toxicity that inhibits plant growth results from inhibition of cell division through induction of chromosomal aberrations.

5.3.2 Growth Retardation

Cr(VI) is known to produce serious damage in living plant cells, but Cr(III) is less toxic because of its extremely low solubility, which prevents leaching into ground water or uptake by plants. At 100 μM of Cr(III), 40% growth retardation occurs, whereas Cr(VI) showed 75% inhibition in shoots and 90% in roots of barley seedlings. At low 'Cr' concentrations, the dry matter content and shoot and root length were found to increase (Bonet et al. 1991). It was also noted that marked decreases in shoot/root ratio resulted from increasing concentrations of chromium (Cary et al. 1997b; Zayed et al. 1998; Patra et al. 2005).

Visual and other symptoms of Cr toxicity in plants are stunted growth, poorly developed root system, curled and discolored leaves (Pratt 1966), chlorosis and narrow leaves (Hunter and Vergnano 1953), chlorotic bands on cereals (Kabata-Pendias and Pendias 1992), and yield reduction (Hara et al. 1976; Hara and Sonoda 1979; Parr and Taylor 1982). Chromium has deleterious effects on plant growth also because it causes perturbations in mineral nutrition. Cr also causes wilting and plasmolysis in root cells (Bassi et al. 1990; McGrath 1995). After exposure to high Cr concentrations, some plants may exhibit brownish red leaves that display small necrotic areas, purpling of basal tissue (Adriano 1986; Hunter and Vergnano 1953), immediate wilting, and plant death (Hara and Sonoda 1979; Parr and Taylor 1982).

Shewry and Peterson (1974) observed that the first toxic effect of Cr(VI) to plants was inhibition of root and shoot growth. Hauschild (1993) has provided the sequence of observed symptoms after Cr exposure in plants: induction of stress compounds (putrescine and chitinase) > inhibition of root growth > visible damage symptoms > leaf growth.

5.3.3 Photosynthetic Inhibition

A symptom of chromium toxicity in plants is induced disorganization of ultrastructure of chloroplast membranes (Sarkar and Jana 1987; Poschenrieder et al. 1991). Chromium toxicity in plants leads to diminished photosynthesis (Austenfeld 1979; Dubey and Rai 1987) accompanying reduced chlorophyll synthesis (Vazquez et al. 1987). This phenomenon results in visual symptoms in plants such as chlorosis, necrosis, and stunted growth (Panda and Patra 2000a; Panda et al. 2003). The inhibition of photosynthesis was due to ultrastructural changes in the chloroplast, viz., severe decreases in granal and stromal lamellae and swelling of thylakoid membranes (Poschenrieder et al. 1991; Bassi et al. 1990; Choudhury and Panda 2004). Such effects are observed in several plants such as *Lemna minor*, *Pistia* spp., *Taxithelium nepalense*, and bean plants. Chromium also causes a decrease in the Hill reaction of chloroplasts and this affects both dark and light reactions (Krupa and Baszynski 1995; Zeid 2001).

5.3.4 Oxidative Stress

Chromium toxicity results in oxidative stress in plants. Such oxidative stress results from the generation of free radicals or reactive oxygen species (ROS) such as O_2^- , H_2O_2 , $^{\bullet}OH$ (Panda and Patra 2000b; Panda and Choudhury 2005). These ROS may produce oxidative damage to biological membranes (caused by lipid peroxidation). The basic cause of chromium toxicity emanates from the process of reduction of Cr(VI) to lower oxidation states (Kawanishi et al. 1986), in which free radicals are generated (Kadiiska et al. 1994; Panda et al. 2003; Choudhury and Panda 2005). The formation of a transient form of Cr(V), during the reduction of Cr(VI) to Cr(III), is thought to be one probable mechanism by which ROS are developed and cause their effects in plants (Kawanishi et al. 1986). The entities responsible for the formation of Cr(V) from Cr(VI) are physiological reducing agents such as NAD(P)H, $FADH_2$, several pentoses, and glutathione (Shi and Dalal 1989). Cr(V) complexes react with H_2O_2 to generate significant amount of $^{\bullet}OH$ radicals, which may directly trigger interactions with DNA and/or induce other toxic effects.

5.3.5 Enzymatic Changes

Several antioxidant enzymes (catalase, peroxidase, glutathione reductase, ascorbate peroxidase, and superoxide dismutase) may scavenge the ROS formed by the presence of Cr. These antioxidants mitigate oxidative damage and reduce stress phenomena. The activity of peroxidase and catalase has been studied in response to chromium toxicity in several plant species: rice, wheat, green gram, and in lower plants like mosses (Panda and Patra 1998; Panda 2003). Results show that the activities of these enzymes may be suppressed or induced. Suppressed enzyme activity was observed in plants grown under conditions of toxic levels of Cr, but simultaneously, the synthesis of other enzymes was stimulated. The suppression and induction vary with the plant species involved. Increased synthesis was observed in catalase and peroxidase activity at 100 μM of Cr(VI), in hydroponically grown wheat seedlings. Cr(III) may also react with the carboxyl and sulphydral groups of enzymes and cause alternation of their structure and activities (Bianchi and Levis 1977; Mohanty et al. 2005, 2008). Although there are several reports of the hyperactivity of antioxidative enzymes in various plants that are under Cu, Pb, Zn stress (Ali et al. 2003; Van Assche and Clijsters 1990), there are few reports available on the role of enzymatic antioxidant systems in protecting plants from ROS stress induced by Cr. This demonstrates the hypothesis of Dong et al. (2007), which is that although antioxidants may alleviate Cr-induced stress, antioxidants may also be a sensitive target of Cr toxicity in plants.

High concentrations of Cr cause protein degradation and inhibit nitrate reductase activity, in some plants (Solomonson and Barber 1990; Vajpayee et al. 1999, 2000). A decline in the content of amino acids such as cysteine (Vajpayee et al. 2001) and increased synthesis of proline were reported to occur at toxic levels of chromium. Moreover, a severe inhibition of cytochrome oxidase activity resulted from the binding of Cr to complex-IV and Cyt-a₃ in the mitochondrial electron transport system

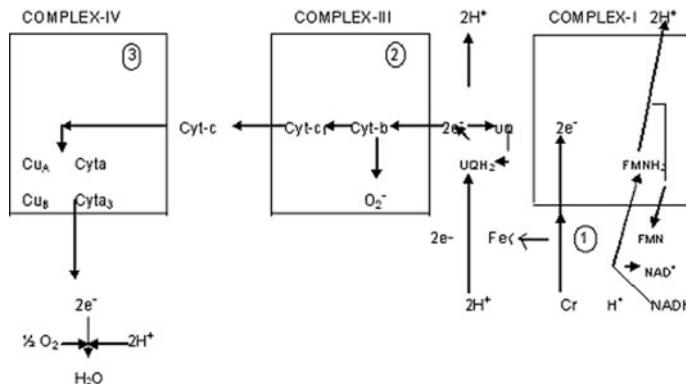


Fig. 1 The electron transport system of plants as influenced by chromium. The *circled numbers* (1, 2, and 3) identify the biochemical sites of action at which chromium may generate its effects (Panda and Choudhury 2005)

(Dixit et al. 2002). The sites in the electron transport chain that may be affected by chromium are depicted in Fig. 1.

Fe-reductase activity was decreased in response to chromium in Fe-deficit plants (Schmidt 1996). Chromium possesses the capacity to degrade δ -amino levulinic acid dehydratase, which is an important enzyme for chlorophyll biosynthesis (Vajpayee et al. 2000).

5.3.6 Macromolecular Damage

Chromium toxicity that produces damage to macromolecules has been observed in several studies. Chromium may inhibit cell division and induce chromosomal aberrations (Liu et al. 1993). Cr(III) and H₂O₂ cause breakage of DNA strands at a pH of 6–8 (Strile et al. 2003). Cr also hampered the replication of DNA by inhibiting transcriptional and translational processes. Binding of chromium ions to DNA molecules is well documented to occur in mammalian (Levis et al. 1975) and hamster cells (Bianchi and Levis 1977). Intracellular Cr(III) may be sequestered by DNA phosphate groups that affect replication and transcription, and may cause mutagenesis (Costa 1997). Cr(III) causes modification of DNA polymerase and other enzyme activities by displacing Mg ions.

5.3.7 Other Phytotoxic Effects

Cr(VI) depresses plant uptake of potassium and impedes H⁺ extrusion coupled to K⁺ uptake across the plasma membrane, and may produce a decrease in the proton gradient and depolarize transmembrane electric potential energy (Zaccheo et al. 1982; Marre et al. 1974). This energy-linked process is believed to be important in regulating certain important physiological processes such as seed germination and stem elongation (Marre 1979). Chromium causes perturbation in the structure of the

Euglena cell nucleus (Fasulo et al. 1983) and in the trifoliate leaves of bush bean (Vazquez et al. 1987).

5.3.8 Plant Response to Heavy Metals

Plants have three basic strategies for growing in metal-contaminated soil. To protect themselves from the toxic effects of heavy metals, plants may either be (a) excluders, (b) indicators, or (c) hyperaccumulators. (a) *Metal excluders* act to prevent metal from entering their aerial plant parts, or they maintain low and constant metal concentrations as they grow in soils having a broad range of metal concentrations. Such plants store absorbed metals primarily in their roots. These plants may alter their membrane permeability, change metal-binding capacity of cell walls, or exude more chelating substances. (b) *Metal indicators* are species which actively accumulate metal in their aerial tissues at levels that generally reflect metal levels in the soil. They tolerate the existing concentration level of metals by producing intracellular metal-binding compounds (chelators) or alter metal compartmentalization patterns by storing metals in non-sensitive parts. (c) Some plant species can concentrate metal in their aerial parts to levels that far exceed soil levels. These are called *hyperaccumulators*. Such plants can absorb high levels of contaminants and concentrate them either in their roots, shoots, and/or leaves (Fig. 2).

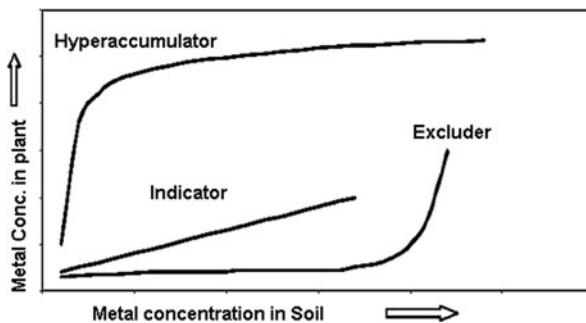


Fig. 2 Conceptual response strategies of metal concentrations in plant tops in relation to increasing total metal concentrations in the soil (Ghosh and Singh 2005a). Notes: *Hyperaccumulators*: The plants that can absorb high levels of contaminants concentrated either in their roots, shoots, and/or leaves. *Indicators*: The tolerant plant species which actively accumulate metal in their aerial tissues and generally reflect metal availability in the soil. *Excluders*: The plants which prevent metal from entering their aerial parts and restrict metal in their roots

6 Technology for Chromium Bioremediation

Heavy metals occur naturally in soils and plants and are integral components of the biosphere. Soil contamination with heavy metals caused by human activities is normally dealt with by transfer of contaminated soil to landfills. However, this

approach is expensive and causes its own problems. Therefore, eco-friendly technologies that offer low-cost alternatives are increasingly being sought to replace the former processes. Bioremediation may constitute such an alternative for the future. Bioremediation is the process of using living organisms, typically plants or microbes, to remove toxic elements from the environment (Kumar et al. 1995; Adler 1996; Cunningham and Ow 1996; Negri and Hunchman 1996; Yang et al. 1996; Kiling 1997). Usually, bioremediation takes advantage of natural processes that already exist within selected organisms. The advantages of in situ bioremediation (bioremediation that takes place at the site of the contamination) are that it is cheaper and it eliminates the need to extract or remove the contaminants, thus resulting in reducing the prospect of exposure to workers. The disadvantages are that the site of bioremediation is not contained, and it is harder to control conditions and monitor progress.

Some bioremediation techniques are described below in greater detail. They are broadly classified into two categories depending on the type of organisms used for remediation.

6.1 Microbial Remediation

Many trials and studies have shown that both prokaryote and eukaryote microorganisms have been successful in achieving recovery of metals from industrial waste streams. In other studies, microbes have been utilized as biofertilizers to stimulate the growth of plants by increasing soil fertility. It is also known that microbes may release metal chelators or metal binders, which can help to increase absorption of minerals from soil and reduce toxic levels of Cr. The different approaches that have utilized microorganisms to achieve remediation are reviewed below.

6.1.1 Biostimulation

Biostimulation is the addition of nutrients, oxygen, or other electron donors and acceptors to a site requiring mitigation of heavy metal contamination, for the purpose of enhancing microbial activity of naturally occurring organisms (Leung 2004). Biostimulation provides the basis for the requirement of retaining viable native populations of specific contaminant-degrading microbes that already exist at the site. Successful biostimulation may require amendment or support to achieve the correct environment for accomplishing the degradation or detoxification of a contaminant to an acceptable regulatory level, within a reasonable time period (Quagraine et al. 2005).

6.1.2 Bioaugmentation

Bioaugmentation is the addition of microorganisms, to those that already exist at a site, that can biotransform or biodegrade contaminants (Quagraine et al. 2005). The added microorganisms may be a completely new species or simply more members

of a species that already exist at the site. A necessary prerequisite for an efficient bioaugmentation would be the presence of nutrients that can stimulate the growth and activity of these “foreign” microorganisms (Quagraine et al. 2005). But the application of this technique for removal of Cr is not currently in regular practice. This method does not currently offer any obvious treatment advantages, in consumption of time and money. Moreover, stimulating indigenous microbial populations does not constitute, at this time, an acceptable treatment of contaminated sites. One concept for the future is to inoculate local microbial cultures with selected foreign microbes that have demonstrated a capability to degrade the contaminants present. Once acclimatized to their new environment, such inoculants may be entertained for use in bioaugmentation. However, there is the need to examine whether these “foreign” microorganisms that are added to tailings in pond water can compete with the indigenous populations or not (Quagraine et al. 2005).

6.1.3 Bacteria

Bacteria are generally the most commonly used organism for bioremediation. However, fungi, algae, and plants have also been used. Bioengineering of bacterial heavy metal resistance genes has produced biosensors for several toxic metals (Ramanathan et al. 1997). Some bacteria have the ability to reduce Cr(VI) and may be ideal for bioremediation of chromate-polluted areas (Otake and Silver 1994; Wakatasuki 1995; Silver and Williams 1984; Loveley et al. 1993). Precipitation of Cr has been reported in anaerobic *Clostridium* and by sulfate-reducing bacteria (Dvorak et al. 1992).

Adsorption of Cr(III) can occur by the heat-dried biomass of the cyanobacterium *Phormidium laminosum* (Sampedro et al. 1995). *Cladophora* accumulated several heavy metals, and this genus accumulated more Cr at a faster uptake rate (72% after 15 min) than it did other metals (Vymazal 1990). Cr(III) was effectively removed (83–99%) in laboratory tests with *Scenedesmus*, *Selenastrum*, and *Chlorella*, whereas Cr(VI) was rather poorly removed (18–22%) (Brady et al. 1994). The removal of Cu, Ni, Al, and Cr from acidic mine wastes by the red algae *Cyanidium caldarium* occurs by cell surface precipitation of metal-sulfide microcrystals (Wood and Wang 1983).

6.1.4 Yeast and Filamentous Fungi

These organisms offer a viable alternative for the bioremediation of soils polluted by Cr (Cervantes et al. 2001). A new siderophore, rhizoferin, has been identified in *Mucorales* that shows increased Cr(III) biosorption (Pillichshammer et al. 1995). Chemically treated mycelia from *Mucor mucedo* and *Rhizomucor miehei* efficiently bind Cr (Wales and Sagar 1990). The biomasses obtained from *Rhizomucor arrhizus*, *Candida tropicalis*, and *Penicillium chrysogenum* were excellent biosorbents of Cr (Volesky and Holan 1995). *S. cerevisiae* and *Candida utilis* have the ability to sorb Cr(VI) and the sorption capacity of dehydrated cells is considerably higher than that of intact cells (Rapoport and Muter 1995). In most cases, Cr accumulation in

the chromate-resistant fungi was lower than in chromate-sensitive strains, but the biosorption and bioaccumulation processes were similar (Czako-Ver et al. 1999). The biosorption ability of chromate-resistant mutants could be combined with their ability to reduce chromate. Chromate-resistant strains of *Aspergillus* spp. (Paknikar and Bhide 1993) and *Candida* spp. (Ramirez et al. 2000), isolated from Cr-polluted environments, have shown Cr(VI) reducing activity. Moreover, there is evidence that the heavy metal-tolerant arbuscular mycorrhizal fungi (AM fungi) could protect plants against the harmful effects of excessive heavy metals.

In heavy metal-contaminated sites, AM fungi improve plant growth and survival by increasing plant access to relatively immobile minerals such as P (Vivas et al. 2003; Misra et al. 2004), and this improves soil texture by binding soil particles into stable aggregates that resist wind and water erosion (Rilling and Steinberg 2002). Moreover, AM fungi are capable of binding heavy metals into roots in ways that restrict their translocation into shoot tissues (Dehn and Schuepp 1989; Kaldorf et al. 1999; Misra et al. 2004). AM fungi play a vital role in metal tolerance (del Val et al. 1999) and accumulation (Jamal et al. 2002), because they store a greater volume of metals in their mycorrhizal structures and in their roots and spores. Several heavy metal-tolerant AM fungi have been isolated from polluted soils. These fungi can be useful for reclamation of such degraded soils, because they are naturally associated with many plant species in heavy metal-polluted soils (Gaur and Adholeya 2004).

Increased root/shoot Cr ratio in AM plants has also been found by Misra et al. (2004) in chromite-mine overburden soil. The change in this ratio may point to other mitigation mechanisms, such as dilution by increased root or shoot growth, exclusion by precipitation into poly-phosphate granules, and compartmentalization (Kaldorf et al. 1999; Turnau et al. 1993). Indirect mitigation mechanisms may occur and include the effect of AM fungi on rhizosphere characteristics such as changes in pH (Li et al. 1991), microbial communities (Olsson et al. 1998), and root-exudation patterns (Laheurte et al. 1990). The use of dead fungal biomass of *Aspergillus niger* for the detoxification of Cr(VI) from contaminated waters has also been studied. Park et al. concluded that the mechanism of Cr(VI) removal by dead fungal biomass such as *A. niger* was a redox reaction. Cr(VI) was reduced to Cr(III) through both direct and indirect mechanisms. The Cr(VI) removal rate was increased with decreased solution pH and with increased Cr(VI) concentration, biomass concentration, and temperature. Dead fungal biomass is abundant, cheap, does not require a continuous nutrient supply for maintaining the cells in good physiological conditions, and dead cells are not subjected to physiological constraints such as metal toxicity.

6.2 Green Remediation

Phytoremediation or “green” remediation is defined as the use of green plants to remove pollutants from the environment or to render them harmless. The generic term ‘phytoremediation’ consists of the Greek prefix *phyto* (plant), attached to the Latin root ‘*remedium*’ (to correct or remove an evil). This technique is a

cost-effective plant-based approach for removal of heavy metals from soil and groundwater (Jena et al. 2004). The success of phytoremediation or phyto-mining depends on the availability of plant species – ideally those native to the region of interest – that are able to tolerate and accumulate high concentrations of heavy metals (Baker and Whiting 2002).

There is currently considerable interest in the use of phytoremediation technology to deal with the problem of chromium- and other heavy metal-contaminated soils, sediments, and water. Although metal-contaminated soil can be remediated by chemical, physical, and biological techniques, the most appropriate technique may be determined by studying the particular category of contamination. Remediation of metal-contaminated soil can be grouped into two categories as defined below (Blaylock and Huang 2000; Cooper et al. 1999; Ghosh and Singh 2005a; Huang et al. 1997).

6.2.1 *Ex Situ* Methods

Ex situ methods require removal of contaminated soil for treatment either on or off site, and then returning the treated soil to the restored site. The conventional *ex situ* methods that are applied to remediate polluted soils relies on excavation and detoxification (physical or chemical destruction). Such treatments may either destroy or may result in the contaminant being solidified or otherwise immobilized. In addition, incineration of contaminants is sometimes used to effect virtual total destruction. The conventional *ex situ* technique is to excavate heavy metal-contaminated soil and then rebury it at a landfill site (McNeil and Waring 1992; Smith 1993). Such offsite burial of contaminated media is often inappropriate because it merely shifts the contamination problem to a new site; moreover, there are hazards associated with the transport and redeposition of contaminated soil.

6.2.2 *In Situ* method

In the *in situ* method, remediation occurs without excavation of a contaminated site. Reed et al. (1992) defined *in situ* remediation technologies as destruction or transformation of the contaminant, immobilization to reduce bioavailability, and separation of the contaminant from the bulk soil. The use of microbial biomass and bioaccumulators helps to capture metals by extracellular precipitation and subsequent intracellular accumulation; thus, the toxic metal ions are immobilized at the site of contamination which reduces their bioavailability. *In situ* techniques are favored over *ex situ* techniques because they are cheaper and are still effective in reducing ecosystem impact. Diluting the heavy metal content of a substrate to a safe level by importing it and mixing it with clean soil is sometimes an alternative for on-site management (Musgrove 1991). On-site containment, with appropriate barriers, provides another alternative that involves covering the soil with inert material.

Although the concept has been informally employed for at least 300 years, the modern concept of using metal-accumulating plants to remove contaminating compounds was first introduced in 1983. This technology can be applied to both organic

and inorganic pollutants that are present in soil (solid substrate), water (liquid substrate), and air. The technique involves the ability of plants to absorb and concentrate elements of heavy metals from contaminated environmental media (soil and water); metals that are candidates for successful uptake by plants includes Se, Hg, Pb, Cr, Cd, Zn, and Fe. There are five categories of phytoremediation techniques: phytoextraction using hyperaccumulator plants, phytovolatilization, rhizofiltration, phytostabilization, and phytodetoxification (Salt et al. 1995, 1998). These processes will be discussed in detail below.

Phytoextraction

Phytoextraction involves using plants that are capable of accumulating metals from contaminated soils, sediments, and water, at high concentrations, into their tissues (Peterson 1975). It is the best approach to remove and isolate soil contaminants without destroying soil structure and fertility. It is also referred to in the literature as phytoaccumulation (Fig. 3) (USPAR 2000). The selected plant absorbs, concentrates, and precipitates the toxic metals and radionuclides from contaminated soils (Brooks et al. 1998) in their biomass. This technique is best suited for the remediation of areas that are diffusely polluted at relatively low concentrations and where contamination rests primarily near the surface (Rulkens et al. 1998). Several approaches have been used, but the main two strategies for phytoextraction are

- Chelate-assisted phytoextraction or induced phytoextraction, in which artificial chelates are added to soil to increase the mobility and uptake of metal contaminant.
- Continuous phytoextraction, in which the removal of metal depends on the natural ability of the plant to remediate; only the number of plant growth repetitions is controlled.

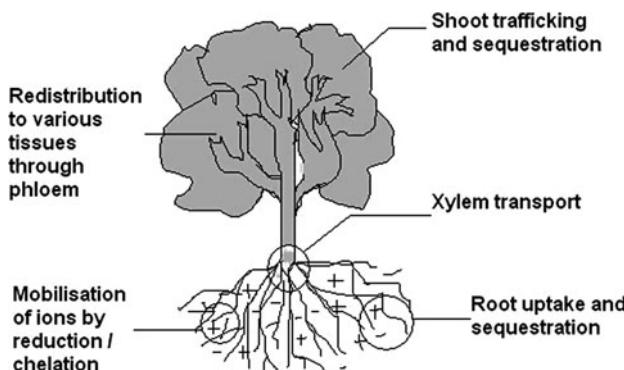


Fig. 3 Pictorial representation of the process of phytoextraction

Hyperaccumulator plants have been used to boost the effectiveness of this technology. To make this technology feasible, the plants must extract large concentrations of heavy metals into their roots, translocate the heavy metals to surface biomass, and produce a large quantity of plant biomass. The removed heavy metals can be recycled through phyto-mining (Nicks and Chamber 1994; Ghosh and Singh 2005a) to produce bio-ore, which is a form of concentrated metal that is produced from the contaminated plant biomass and may be sold (Fig. 4). Factors such as plant growth rate, element selectivity, resistance to disease, and method of harvesting are also important factors in selecting candidate plants as hyperaccumulators. Factors like slow growth, shallow root systems, small biomass production, or difficulty in final disposal limit the use of hyperaccumulator species. Plants such as *Ipomoea carnea*, *Datura innoxia*, *Phragmites karka*, *Cassia tora*, *Lantana camara*, *Brassica juncea*, *Brassica campestris*, *Leersia hexandra*, *Convolvulus arvensis*, *Albizia amara*, *Cynodon dactylon*, and *Pluchea indica* are being studied for Cr hyperaccumulation capacity by several workers (Torresdey et al. 2004; Shanker et al. 2005b; Ghosh and Singh 2005b; Sampanpanish et al. 2006; Zhuang et al. 2007). Some plants can accumulate remarkable levels (100- to 1,000-fold the levels normally found in most species) of heavy metals. This striking phenomenon, known

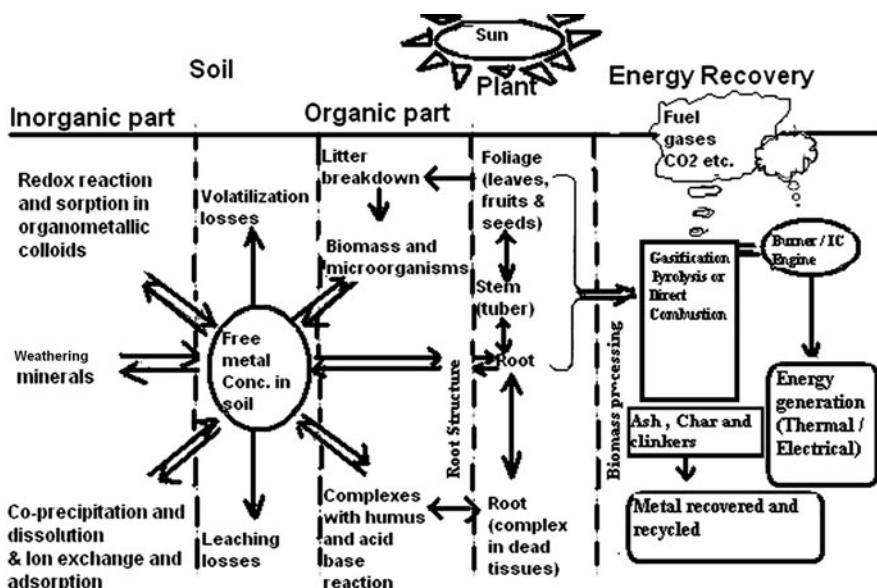


Fig. 4 The soil, plant, and energy recovery system depicting the key components concerned with the mass transfer and dynamics of phytoextraction (Ghosh and Singh 2005a). The soil system involves the generation of free-metal concentration in soil from its inorganic and organic fractions. The plant system extracts (phytoextraction) large concentrations of heavy metals into their roots, stems, and foliage and concentrates these metals in the biomass fraction. The energy recovery system recovers heavy metals from plant biomass for production of bio-ore and generates energy for human needs by thermo-chemical conversion of plant biomass

as metal hyperaccumulation (i.e., the ability to accumulate at least 0.1% of the leaf dry weight as a heavy metal) (Rajakaruna et al. 2006), is only exhibited by <0.2% of angiosperms (Baker and Whiting 2002), making the selection of native species for phytoremediation efforts a difficult task. One promising species, *Typha angustifolia*, has showed high tolerance to Cr (Dong et al. 2007).

Natural Phytoextraction

In the natural setting, certain plants have been identified, which have the potential to take heavy metals up. At least 45 plant families have been identified to have plant species that can hyperaccumulate contaminants. Some of these families are: Brassicaceae, Fabaceae, Euphorbiaceae, Asteraceae, Lamiaceae and Scrophulariaceae (Salt et al. 1998; Dushenkov 2003). Among the best-known hyperaccumulator species is *Thlaspi caerulescens*, commonly known as alpine pennycress (Kochian 1996). It is impressive that without showing injury this species accumulated up to 26,000 mg/kg Zn and up to 22% of soil exchangeable Cd from a contaminated site (Brown et al. 1995; Gerard et al. 2000). *Brassica juncea*, commonly called Indian mustard, has also been found to have the ability to transport lead from its roots to the shoots.

Results of studies performed worldwide have shown that certain plants will tolerate high levels of metals in their tissues. For example, Ni is known to reside at concentrations of >1,000 mg/kg in more than 320 plant species (spp.). Besides Ni, high concentrations of other elements have also been found in many plant species (number of species given in the parenthesis) as follows: Co (30 spp.), Cu (34 spp.), Se (20 spp.), Pb (14 spp.), and Cd (1 sp.) (Reeves and Baker 2000). Concentrations exceeding 10,000 mg/kg have been recorded for Zn (11 spp.) and Mn (10 spp.). The hyperaccumulation threshold levels of these elements have been set higher because their normal ranges in plants (20–500 mg/kg) are much higher than that for the other heavy metals (Reeves 2003). Aquatic plants such as the floating *Eichornia crassipes* (water hyacinth) (Mohanty and Patra 2007), *Lemna minor* (duckweed), and *Azolla pinnata* (water velvet) have been investigated for use in rhizofiltration, phytodegradation, and phytoextraction (Salt et al. 1997).

Induced Phytoextraction or Chelate-assisted Phytoextraction

Within the plant cell, heavy metal residues may trigger the production of oligopeptide ligands known as phytochelatins (PCs) and metallothioneins (MTs) (Ghosh and Singh 2005a). These peptides bind and form stable complexes with the heavy metal and thus neutralize the toxicity of the metal ions. PCs are synthesized with glutathione as a building block and results in a peptide with the structure: Gly-(γ -Glu-Cys- n), {where $n = 2-11$ }. Appearance of phytochelating ligands has been reported in hundreds of plant species exposed to heavy metals. MTs are small gene encoded Cys-rich polypeptides. PCs are functionally equivalent to MTs. In addition to use of PCs, one can enhance uptake effectiveness by adding the synthetic chelate EDTA to the soil (Huang et al. 1997). Similar results can be achieved by using citric acid to enhance uranium uptake. The results of Huang et al. (1997) showed

that chelates enhance or facilitate Pb transport into the xylem, and increase lead translocation from roots to shoots. For the chelates tested, the order of effectiveness in increasing Pb desorption from the soil was EDTA > hydroxyethylethylene-diaminetriacetic acid (HEDTA) > diethylenetriaminepentaacetic acid (DTPA) > ethylenediamine di (*o*-hydroxyphenylacetic acid) (EDDHA) (Huang et al. 1997).

Limitations of Phytoextraction

Phytoextraction and plant-assisted bioremediation are most effective in the removal of contaminants if soil contamination resides within 3 ft of the surface and if ground-water is within 10 ft of the surface. It is uncertain whether an approach based on chemical chelators is practical for improving phytoextraction, since chemical chelators are also toxic to plants and may increase the uptake of metals but decrease plant growth.

Phytovolatilization

Phytovolatilization is another type of phytoremediation. Phytovolatilization involves the use of plants to take up contaminants from the soil, transform them into a volatile form, and then transpire them into the atmosphere. Phytovolatilization occurs as growing trees and other plants take up water and any associated organic and inorganic contaminants. Some of these contaminants can pass through plant membranes and ultimately to the leaves, where they can volatilize into the atmosphere at comparatively low concentrations (Fig. 5) (Mueller et al. 1999).

Phytovolatilization has been primarily used for the removal of mercury; the mercuric ion is transformed in plants into the less toxic elemental mercury. The disadvantage of this process is that mercury released into the atmosphere is likely to be recycled by precipitation and then redeposited back into ecosystem (Henry 2000). Bioremediation of Se and As is also possible using phytovolatilization technique.

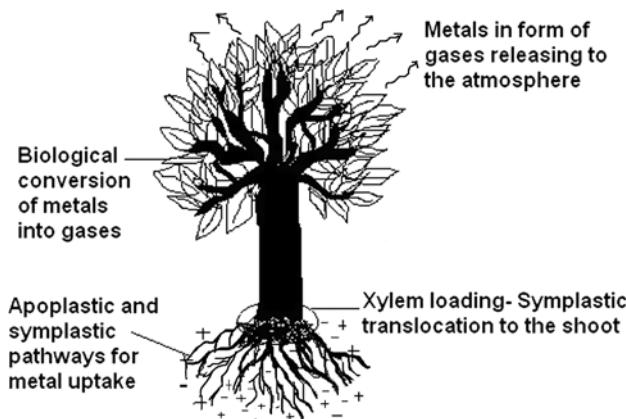


Fig. 5 Pictorial representation of the process of phytovolatilization

Rhizofiltration

Rhizofiltration is a technique that can remove contaminants from flowing water and aqueous waste streams by processing them through the extensive root system of plants. Several aquatic plant species and hyperaccumulator plants have been used to remove heavy metals from waste stream/water.

Rhizofiltration is defined as the use of plants, both terrestrial and aquatic, to absorb, concentrate, and precipitate contaminants from polluted aqueous sources that have a low contaminant concentration in their roots. Rhizofiltration can be used to partially treat industrial discharge, agricultural runoff, or acid-mine drainage. It can be used to remove lead, cadmium, copper, nickel, zinc, and chromium, which are primarily retained within plant roots (Chaudhury et al. 1998; USPAR 2000). The advantages of rhizofiltration include the fact that (a) it can be used in in situ or ex situ applications and (b) with non-hyperaccumulator plant species. Several plants (e.g., sunflower, Indian mustard, tobacco, rye, spinach, and corn) have been studied for their ability to remove lead from effluents by rhizofiltration. Sunflower has the greatest ability to remove lead contamination among the tested species. Wetland plant species such as water hyacinth (*Eichornia crassipes*), duckweed, smooth cord grass, smartweed, *Thlaspi caerulescens*, some members of Brassicaceae family have also been used to remove heavy metals, such as As(V), Cd(II), Cr(VI), Cu(II), Ni(II), Se(VI), Zn, and Pb.

Phytostabilization

Phytostabilization is the process in which plants are used to transform soil metals to less toxic forms, but without removing the metal from the soil (Fig. 6). It is mainly used for remediation of soil, sediment, and sludges and depends on the ability of plant roots to limit contaminant mobility and bioavailability in the soil (USPAR 2000; Mueller et al. 1999). Phytostabilization can occur through sorption, precipitation, complexation, or metal valence reduction (Salt et al. 1995). The primary purpose of the plant in fulfilling its phytostabilizing role is to decrease the amount of water that percolates through the soil matrix. This, in turn, slows or prevents the formation of hazardous leachate and prevents soil erosion and the distribution of the toxic metal to other areas. It is the dense root system of plants that stabilizes the soil and prevents erosion. This approach is very effective when rapid immobilization is needed to preserve ground and surface water, and when disposal of biomass is not required.

Phytodetoxification

This method is an in situ process, which involves detoxification of heavy metals through plant-based chelation, reduction, and oxidation mechanisms. Several plant species and algae have been used in the reduction of chromium(VI) to Cr(V), and eventually to Cr(III). Several vegetable crops and wetland plant species are also used for remediation. Metal chelators like EDTA, DTPA, EDDHA, organic acids

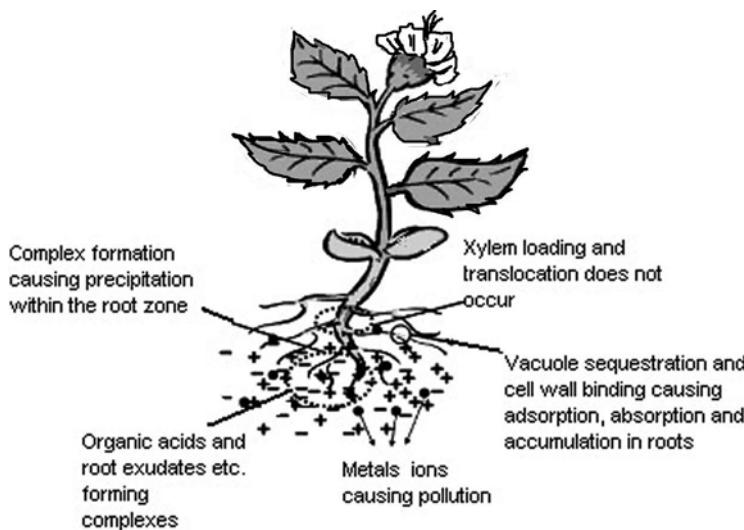


Fig. 6 Pictorial representation of the process of phytostabilization

(carboxylic acids, salicylic acids, maleic acid), and glycine are also useful for heavy metals remediation (Henry 2000; Salt et al. 1998).

6.2.3 Genetic Engineering to Improve Phytoremediation

To breed plants of higher biomass that have superior phytoremediation potential is an attractive avenue for improving phytoremediation. The high biomass and productivity of a plant is genetically controlled. Therefore introduction of such desired genes to a plant (transgenic plant) will improve the phytoremediation activity. Notwithstanding, it is crucially important to identify appropriate plant genotypes/cultivars that are resistant/tolerant to Cr, or to other contaminants, so that new and relevant genes become available for use in environmental remediation. To achieve a better understanding of the physiological and biochemical mechanisms of heavy metal tolerance/resistance in plants, researches in the related areas are essential. These research areas are fundamental for discovering or creating new metal-resistant plant species. Such work has been undertaken by Dong et al. (2007). These authors are using *Typha angustifolia* plant species that grow in Cr-contaminated areas and demonstrate high resistance to Cr stress.

7 Summary

Chromium is an important toxic environmental pollutant. Chromium pollution results largely from industrial activities, but other natural and anthropogenic sources also contribute to the problem. Plants that are exposed to environmental

contamination by chromium are affected in diverse ways, including a tendency to suffer metabolic stress. The stress imposed by Cr exposure also extends to oxidative metabolic stress in plants that leads to the generation of active toxic oxygen free radicals. Such active free radicals degrade essential biomolecules and distort plant biological membranes. In this chapter, we describe sources of environmental chromium contamination, and provide information about the toxic impact of chromium on plant growth and metabolism. In addition, we address different phytoremediation processes that are being studied for use worldwide, in contaminated regions, to address and mitigate Cr pollution.

There has been a long history of attempts to successfully mitigate the toxic effects of chromium-contaminated soil on plants and other organisms. One common approach, the shifting of polluted soil to landfills, is expensive and imposes environmental risks and health hazards of its own. Therefore, alternative eco-friendly bioremediation approaches are much in demand for cleaning chromium-polluted areas. To achieve its cleaning effects, bioremediation utilizes living organisms (bacteria, algae, fungi, and plants) that are capable of absorbing and processing chromium residues in ways which amend or eliminate it. Phytoremediation (bioremediation with plants) techniques are increasingly being used to reduce heavy metal contamination and to minimize the hazards of heavy metal toxicity. To achieve this, several processes, viz., rhizofiltration, phytoextraction, phytodetoxification, phytostabilization, and phytovolatilization, have been developed and are showing utility in practice, or promise. Sources of new native hyperaccumulator plants for use at contaminated sites are needed and constitute a key goal of ongoing phytoremediation research programs. Such new plants are needed to enhance the attractiveness of phytoremediation as an effective, affordable, and eco-friendly technique to achieve successful clean-up of metal-contaminated sites worldwide.

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The Effects of Radionuclides on Animal Behavior

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1 Introduction

Behavior refers to the observable or measurable actions or reactions of an organism (movements, physiological alterations, verbal expression, etc.) in response to a stimulus originating from its environment (Bone and Moore 2008). Animals express several types of behavior including sexual, reproductive, social (aggression, maternal relationship, etc.), activity (locomotion, feeding, defence and avoidance responses) and cognitive behaviors (attention, learning, memory) (Zala and Penn 2004).

Behavior is regulated by several body systems. These include the sensorial system (chemoreception), nervous system (production of neurotransmitters including acetylcholine), endocrine system and oxidative and metabolic activities (oxygen consumption, lipids, glycogen). Even subtle disturbances in these systems may translate into serious behavioral aberrations, which can have severe implications for survival (Baatrup 2009). Behavior represents the culmination of all the anatomical adaptations and physiological processes that occur within an organism. Behavioral adaptations, along with morphological and physiological adaptations, may occur that increase the fitness of individuals and, through natural selection, the evolution of the species (Bone and Moore 2008).

Behavioral data are difficult to obtain and are often criticized because of their high variability. In addition, laboratory experiments often lack natural ecological realism, which can result in artefacts that make measuring behavior in the field difficult (Zala and Penn 2004). However, standardization of methods is improving, and behavioral testing methods have the advantage of being non-destructive and inexpensive. Moreover, most behavioral measurements induce minimal stress in test organisms and may be repeated on the same individuals, which suggests that behavioral assays could be more powerful than other methods (Kavlock et al. 1996; Little and Finger 1990).

For decades, direct mortality has been a primary metric for assessing the effects of chemical contamination of ecosystems. Ecotoxicologists were among the first to recognize that behavioral measures may have value in the study of sublethal effects of a pollutant, because they may have high sensitivity to changes in the steady state of an organism, compared to other endpoints (Peakall 1996). Moreover, behavioral changes have great potential as biomarkers of internal and external stress in animals, because behavior represents both the physical manifestation of the animal's internal neuronal, metabolic and endocrine processes, and the integrated physiological response to its environment (Clotfelter et al. 2004). Therefore, behavioral measures could be more relevant than ones based on biochemical or physiological parameters (Zala and Penn 2004).

Although behavioral studies conjoined with measures of exposure to contaminants are increasing, few studies have used behavior as an endpoint following exposures to radioactive contaminants. This is unfortunate, because the nuclear industry is expanding worldwide. Several nuclear applications, including nuclear-based energy production, medicine and research, tend to increase the environmental concentrations of some radioactive metals, such as uranium, caesium, cadmium and cobalt (IUPAC 2004). These radioactive metals have many uses in the nuclear industry. Uranium is used in the nuclear fuel cycle as an important source of energy derived from its spontaneous radioactive disintegrations and its fissile properties. Cadmium is used in the form of control rods that regulate neutron flux in reactors. Radioactive cadmium may be formed from unavoidable neutron activation of stable cadmium, as well as from the activation of other stable metals in the core. Cobalt is an essential element present in organisms as vitamin B₁₂. Its radioisotopes, ⁶⁰Co and ⁵⁸Co, are among the main activation products found in the liquid wastes of nuclear power plants, while ⁶⁰Co is largely used in medicine and industry (gammagraphy, sterilization). Caesium is produced by the fission of uranium in nuclear reactors and is mainly used in radiotherapy. Moreover, the radioisotopes ¹³⁴Cs and ¹³⁷Cs are the principal radionuclides measured from fallout of nuclear weapon tests and some nuclear accidents, most notably the Chernobyl disaster.

There are studies in the literature that have addressed the effects of these foregoing elements on behavior in the context of epidemiological surveys of exposed human populations or in laboratory experiments, primarily using rodents, fish, birds and invertebrates as biological models. Therefore, the purpose of this review is to provide an overview of the current literature that focuses on the chemo- and radio-toxicological effects of uranium, caesium, cadmium and cobalt on behavior; the review includes the effects of these elements on the potential underlying mechanisms of behavioral alterations and the behavioral parameters measured on the studied organisms.

2 Link Between Alteration of Physiological Mechanisms and Behavioral Effects

Behavior results from interactions between organisms and their external environment and represents the integration of physiological processes and of mechanisms happening at the subcellular level. A conceptualization of events that form the mechanistic basis of behavior is presented in Fig. 1.

When the environment is modified, any of the processes depicted in Fig. 1 may be affected in a sequential manner, from the disruption of systems receiving the information (e.g., olfactory information) to downstream neurochemical and hormonal mechanisms. An understanding of the mechanisms that control organismal behavior relies on the study of neurochemical and hormonal processes and of molecules involved in the regulation of neuronal activity, including neurotransmitters.

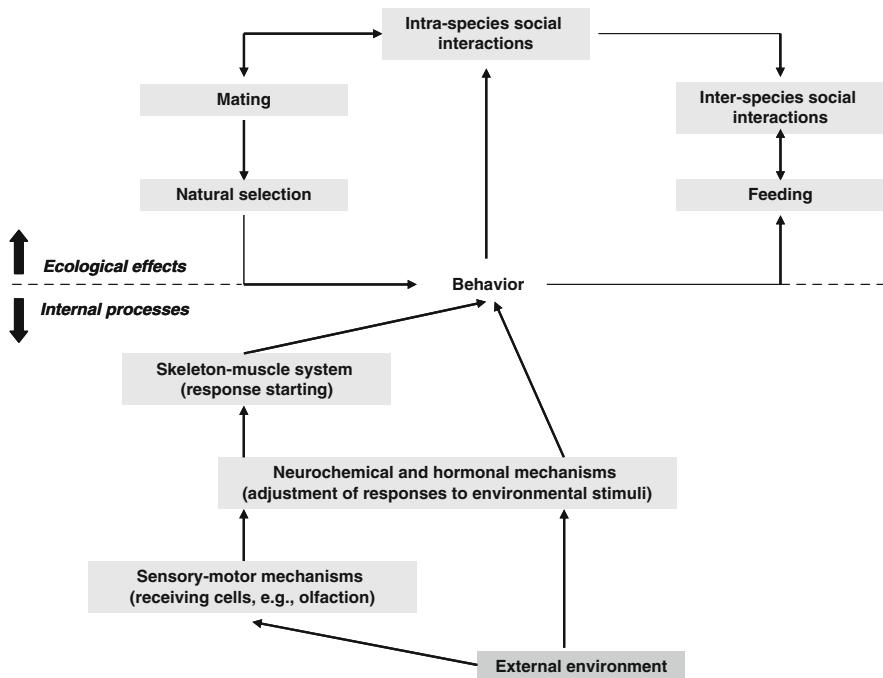


Fig. 1 Relationships between processes that control behavior and ecological effects that may result from behavioral disruption (adapted from Grue et al. 2002)

In this section, we address the description of potential mechanisms underlying behavioral alterations. Behavior is a product of the integration of many physiological systems, namely the sensory, hormonal, neurological, oxidative and metabolic systems. In this review, we address and focus on such system effects in the context of the elements used by the nuclear industry (uranium, caesium, cadmium and cobalt). Broader and exhaustive reviews of this literature on metals in general have been described elsewhere (Baatrup 1991; Clotfelter et al. 2004; Nordberg et al. 2007; Peakall 1996; Scott and Sloman 2004; Zala and Penn 2004; Zalups and Koropatnick 2000).

2.1 Disruption of Sensorial Activity

In fish, chemoreception is very well developed and plays an important role in their response to the environment. Fish rely on olfaction in predator avoidance, reaction to alarm cues and reproduction (Chivers and Smith 1998; Døving and Lastein 2009). In several studies, the effects of non-radioactive metals (e.g., cadmium, copper, zinc, nickel, manganese) have been examined on fish olfaction. The olfactory system is comprised of an olfactory epithelium, the rosette, which contains several ciliated receptor cells linked to the olfactory bulb by the olfactory nerve (Collin 2007).

Receptor cells are bipolar neurons that are in direct contact with the environment and can therefore serve as a portal for metals to enter the brain. In fish, exposure to waterborne cadmium at environmentally relevant levels caused the deposition of cadmium within olfactory sensory neurons (Blechinger et al. 2007; Scott et al. 2003). In rats, cadmium is preferentially accumulated in the brain, since this metal is transported along olfactory neurons by axonal transport mechanisms (Tallkvist et al. 2002).

In Colorado pikeminnow, *Ptychocheilus lucius*, copper accumulation in primary neurones led to the degeneration of ciliated olfactory receptor cells, but this phenomenon was reversible when fishes were placed in an uncontaminated environment (Beyers and Farmer 2001). This transitory capacity of sacrificing peripheral olfactory receptors could give a selective advantage to these fish species. However, reversibility is not always observed. A brief cadmium exposure in zebrafish larvae resulted in long-term deficits in olfaction that resulted in a reduction in response to alarm cues. These response reductions even occurred after a depuration period (Blechinger et al. 2007), probably from necrosis of the olfactory epithelium cells and alterations in the ciliated sensory cells of the olfactory pit (Matz and Krone 2007).

Other sensorial systems may also be disrupted by metals, e.g., low concentrations of cadmium induced histological alterations of the trunk lateral neuromasts in the sea bass, *Dicentrarchus labrax* (Faucher et al. 2006).

The effects of radionuclides on olfaction of fish or other vertebrates have been infrequently studied. However, a disruption of the expression of genes (*or111-7* and *or-102-5*) coding for olfactory receptors was shown in the zebrafish, *Danio rerio*, exposed to depleted uranium, together with an alteration of the ultrastructure of the olfactory bulb (Lerebours et al. 2010).

In rats, uranium has been proposed to enter the brain, not only by the common systemic routes of exposure, but also by a specific inhalation exposure route, the olfactory pathway. Hence, the inhalation of depleted uranium particles in rats led to uranium accumulation in the olfactory bulb and brain, and indicated the existence of a potential transfer pathway to the brain (Monleau et al. 2005). This accumulation of uranium affected locomotor and memory functions. Tournier et al. (2009) confirmed the existence of this olfactory pathway that led to depleted uranium accumulation, and their results showed a specific favoured frontal brain accumulation of the inhaled uranium in rats, mainly in the olfactory bulbs and tubercles, frontal cortex and hypothalamus.

2.2 Neurological Dysfunction

Cholinergic transmission plays an important role in neurocognitive functions and muscular contraction mechanisms and is affected in senile dementia pathologies. Cholinergic neurotransmission involves acetylcholine (ACh) synthesis and release. Once exocytosed, ACh can be hydrolysed by acetylcholinesterase (AChE) on post-synaptic membranes. AChE activity is a commonly used biomarker to assess altered neural functions in brain.

Brain neurotransmitter levels and enzymatic functions have been shown to correlate with behavior. Several studies on pesticides, including organophosphates and carbamates, displayed relationships between the inhibition of AChE and behavioral alterations in fishes, including rainbow trout, *Oncorhynchus mykiss* (Beauvais et al. 2000, 2001; Brewer et al. 2001), and zebrafish (Linney et al. 2004; Roex et al. 2003).

Data on similar effects caused by radionuclides are more scarce. The neurotoxic effects of uranium, particularly its implications for neurotransmission, have, however, been studied. In uranium-exposed zebrafish, a decrease of brain AChE was first observed after 36 h exposure, followed by an increase of the activity at 5–20 days (Barillet et al. 2007). Effects were identical for depleted and enriched uranium, leading to the conclusion that the chemotoxicity of this element is more important than its radiotoxicity. The consequences of AChE inhibition have been demonstrated using *ache* zebrafish mutants that possess no AChE activity: effects are a decrease in mobility, rapidly leading to total immobility (Cousin et al. 2005). The phenotype of these uncontaminated mutants was modified at the behavioral and structural levels, with a muscular disorganization capable of evoking a myopathy. Such a disorganization of muscular fibres was also observed in wild zebrafish exposed to uranium (Barillet et al. 2007), which could be a consequence of AChE inhibition observed in short-term responses. Such alterations of muscular ultrastructure may lead to effects on fish swimming behavior.

In rats, daily intramuscular injection with depleted uranium for 7 days increased AChE activity in the cortex and was associated with sensory-motor alterations (Abou-Donia et al. 2002). In contrast, AChE levels were decreased only in the cortex of rat brain after 9 months of exposure to 40 mg/L of depleted uranium in drinking water (Bensoussan et al. 2009). These results showed that the cholinergic system is affected by the chemotoxicity of uranium.

Neurotransmitters, other than ACh (indirectly measured by AChE), have important roles in neurocognitive functions. In rats, chronic exposure to depleted uranium contamination disrupted the metabolism of dopamine, an essential neurotransmitter that controls locomotion (Bussy et al. 2006). Similarly, the turn-over of serotonin, a neurotransmitter involved in the sleeping-wake cycle, anxiety and depression, was disrupted by a 9-month exposure of rats to depleted uranium contamination (Bussy et al. 2006).

Non-radioactive metals may also have multiple targets in an organism: cadmium exposure of the freshwater mussel, *Anodonta cygnea*, caused changes in filtering behavior, decreased the serotonin and dopamine levels in the central nervous system (Salanki and Hiripi 1990) and also decreased the brain AChE level (Salanki et al. 1993).

2.3 Endocrine Disruption

In some studies, a relationship between hormone levels and behavior was demonstrated, indicating that a deregulation of the endocrine system could lead to behavioral effects (reviewed in Scott and Sloman 2004). Also available are data for metals on the disruption of the hypothalamo-pituitary-interrenal (HPI) axis that

controls the cortisol level, a hormone involved in the stress response. Cadmium exposure of juvenile trout induced an inhibition of the cortisol increase that normally occurred during predation, leading to an inhibition of antipredatory behavior (Scott et al. 2003). Metals also disrupt other hormones, such as growth or thyroid hormones, which play an important role in the migratory behavior in fishes (Comeau et al. 2001). Sexual hormones may also be affected, as was demonstrated for cadmium, which induced a decrease in the transcriptional activity of the estradiol receptor in trout (Vetillard and Bailhache 2005). However, no data are available for radionuclides.

2.4 Oxidative Disruption

Behavioral alterations can cause complex molecular and cellular changes. The brain is highly sensitive to oxidative stress because its antioxidant defences are poorly developed; paradoxically, neuronal tissue is rich in polyunsaturated fatty acids, the main target of lipid peroxidation. In some studies, the role manifested by oxidative stress on behavioral alterations has been observed after metal exposure. Cadmium induced oxidative stress in the central nervous system and induced locomotor dysfunctions; treatment with the antioxidant vitamin E improved these dysfunctions (Ali et al. 1993). After depleted uranium exposure, an increase in lipid peroxidation in rat brain was observed, suggesting damage had occurred to the cell membrane by induction of oxidative stress and production of free radicals (Briner and Murray 2005). Metals and radionuclides, by inducing oxidative stress, can accelerate aging and the development of several diseases (notably neurodegenerative diseases) that are linked to free-radical production (Migliore and Coppedè 2009).

2.5 Metabolic Disruption

Exposure to toxicants can disrupt various aspects of metabolism in fish, from individual (metabolic rate, swimming activity) to tissue responses (substrate availability, enzyme activity), and any of these may translate into a behavioral response (Scott and Sloman 2004).

Fish, like rainbow trout, accumulate metals (cobalt and cadmium) in their gills (Richards et al. 2001); this is likely to alter respiration and therefore behavior. Attempts have been made to relate physiological dysfunctions to behavioral state that result from metal exposure. In rainbow trout exposed to cadmium, appetite decreased and Na^+/K^+ balance was disrupted, but neither O_2 consumption rate nor swimming speed was affected, unlike copper, which decreased both parameters (McGeer et al. 2000).

Several pollutants have been shown to alter levels of metabolic substrates. Cobalt decreased the basal plasma levels of glucose in *Cyprinus carpio*, probably by reducing the rate of gluconeogenesis (Hertz et al. 1989). Cadmium inhibited the cortisol response of rainbow trout to an alarm substance; the authors hypothesized that glucose synthesis would be impaired as a result (Scott et al. 2003). Cobalt decreased

muscle glycogen content and increased lactic acid levels in the blood of the tropical teleost, *Colisa fasciatus*, probably from an increase of catecholamine secretion (Nath and Kumar 1988). A subsequent decrease in available energy could have consequences on fish behavior.

The specific mechanisms by which pollutants alter metabolic substrate availability are unclear, but the observed effects probably reflect actions on enzymes that participate in metabolic activity and/or in protein metabolism (reviewed in Scott and Sloman 2004).

3 Behavioral Responses in Organisms

In this section, we review the known effects of major pollutants (uranium, caesium, cadmium and cobalt) on the behavior of humans, rodents, fish and wildlife species that encounter nuclear applications or nuclear products. Because information on the radioactive forms of these elements is not always available, particularly for cadmium and cobalt, we also cite literature references that pertain to the effects of non-radioactive forms of these elements.

3.1 Humans

3.1.1 Uranium

An extra-pyramidal syndrome (dysfunction of motricity control) that evolves over several years has been described in humans; symptoms of the syndrome include ataxia (walking trouble), nystagmus (involuntary oscillation movement of globe eye) and peripheral neuropathy. In one case that lacked any etiologic causes, these symptoms occurred during the first 3 years of the disease and were attributed to the regular hand manipulation of an uranium rod (Goasguen et al. 1982). Howland (1949) reported cases of persons accidentally contaminated with uranium, who showed behavioral problems the week after the accident; however, the behavioral responses could be attributed to fear alone. The individuals exposed to the contamination showed nervousness, unusual hyperactivity and apprehension, with exaggeration of facial and verbal expressions, which sometimes extended to incoherence. An epidemiologic study on uranium miners in Bohemia disclosed a significant increase of homicides and mental disorders compared to the general population (Tomasek et al. 1994). However, the authors of this study took into account neither the psychogenic factors linked to working conditions, nor the implications of multi-pollution resulting from these miners being also exposed to high concentrations of radon and arsenic.

During the Gulf War, there were reports of soldiers being injured by depleted uranium fragments, which sometimes became permanently embedded in their bodies. Such fragments may represent a source of chronic uranium contamination and potential injury. Injured veterans display increased uranium concentrations in excreted urine, but this occurs without nephrotoxic symptomatology. However, a neurocognitive examination showed a statistical relationship between uranium

concentration in urine and decreased performance on tests designed to evaluate neurocognition. The authors suggest that at this contamination level, the kidney is not the critical target organ, and rather that the neurological or reproductive systems could be the firsts to be disrupted (McDiarmid et al. 2000).

All of the effects described in this section are primarily attributed to the chemotoxicity of uranium.

3.1.2 Caesium

Several studies performed in the years following the Chernobyl accident, in 1986, showed neurological and psychological illnesses associated with radioactive caesium (^{137}Cs) exposure in clean-up personnel (“liquidators”) and people living in the contaminated areas. Among the Kirghizstan liquidators, the most significant observed effects were increased nervous system diseases and mental problems. Between 1989 and 1994, the highest cause of mortality among this liquidator population was suicide (23.2%) (Kamarli and Abdulina 1996). Moreover, a significant relationship was demonstrated for liquidators between the radiation dose levels to which they were exposed and mental disorders (Ivanov et al. 2000).

3.1.3 Non-radioactive Cadmium

At the cellular level, the effects of cadmium are similar to cobalt, with both being powerful inhibitors of several ion channels in neurons and in glial cells. However, although the *in vitro* action of cadmium on neuronal physiology has been well described, it has been demonstrated in a few studies that cadmium exposure could also alter central nervous system function. Because the half-life of cadmium’s residence in humans is 15–20 years, its concentration in hair is a useful criterion to establish intoxication level. Studies of exposed children showed that high cadmium concentrations in hair are associated with learning difficulties or mental retardation (Jiang et al. 1990). In rodents (Section 2.1), cadmium is known to penetrate the brain via the nasal route through olfactory neurons. Such contamination of the olfactory epithelium probably explains why the sense of smell is altered (anosomy) among cadmium–nickel battery-factory workers (Sulkowski et al. 2000). Cadmium also slows psychomotor functions and decreases the capacity of concentration among chronically exposed individuals (Hart et al. 1989).

3.1.4 Non-radioactive Cobalt

Cobalt is the constitutive element of B_{12} vitamin (cobalamine) and plays an important role in nervous system function. Exposure to cobalt-contaminated particles by inhalation may result in neurotoxicity. Such atmospheric pollutants can directly enter the brain via olfactory neurons, and cobalt is known to accumulate in olfactory bulbs. Moreover, memory deficits were observed in people exposed to cobalt particles. In one study, the pineal gland, or epiphysis, contained 1.43 times more cobalt than did other brain structures (Jordan et al. 1997). However, measurements of trace elements in serum of aged patients showed that Alzheimer patients had

significantly lower cobalt concentrations compared to age-matched subjects, suggesting that cobalt could actually act to protect some cognitive functions (Smorgon et al. 2004).

3.2 Rodents

Epidemiologic studies conducted on humans do not always show a relationship between neurobehavioral problems and aetiological factors, because it is difficult to control all of the environmental parameters involved. However, certain genetic parameters can be controlled in experimental animal models. The nature of behavioral alterations can be quantified in properly conceived and conducted neurobehavioral experiments, and such tests are capable of identifying specific toxic effects on the central nervous system. Rodents, in particular, have been used in several types of experiments to study behavioral responses. As a general rule, neurocognitive deficits are more important in juveniles than in adults.

3.2.1 Uranium

The presence of uranium in cerebral structures may have significant consequences for the central nervous system, although most effects derive from chemo- rather than radiotoxicity. The excitability of the hippocampal neurons of rats was decreased 6 months after exposure to depleted uranium. The authors suggest that the hippocampus could participate in cognitive deficits, because it is implicated in learning and memories (Pellmar et al. 1999). Several behavioral studies on rodents showed alterations in cognitive behavior and affected locomotor capacity after chronic or acute exposures to depleted uranium. Alteration of spatial memory and learning was observed in rats after 3 months of exposure by ingestion (Albina et al. 2005; Belles et al. 2005). In another study, hyperactivity in rats was observed after short (2 weeks) and longer (6 months) exposures (Briner and Murray 2005). Sensory-motor deficits in rats were also observed in yet another study (Abou-Donia et al. 2002). After an acute exposure to depleted uranium, rats showed a modification in feeding and rapid eye movement sleep (REM sleep), suggesting respective damage to the hypothalamus and hippocampus had occurred (Lestaev et al. 2005a).

During chronic exposure to 40 mg/L via drinking water, enriched uranium (EU), in contrast to depleted uranium (DU), provoked a disorder of the sleep-wake cycle in adult male rats. An increase of the REM sleep, after exposures of 1, 1.5 or 2 months, was observed only with EU, but this effect disappeared when the exposure was prolonged to 3 months (Houpert et al. 2005; Lestaev et al. 2005b). In addition, the spatial working memory and the anxiety of rats were increased by an exposure of 1.5 months to EU, whereas DU had no effect (Houpert et al. 2005). Other experimental results showed that chronic exposure to DU induced effects that counteracted oxidative stress and produced an increase of antioxidant agents in rat brain. In contrast, EU decreased these effects, and EU, but not DU, increased lipid peroxidation (Lestaev et al. 2009). The authors suggested that the chemical activity of uranium

induces a compensatory response to limit oxidative stress, and radiological activity of uranium facilitates, or at least does not inhibit, this oxidative stress. This result could explain the different behavioral results mentioned above that were obtained from DU and EU studies (Houpert et al. 2005; Lestaev et al. 2005b). All of these results indicate that the rat brain presents differential sensitivity to uranium that depends on the origin of the toxic effect (*i.e.*, chemo- or radiotoxicity).

3.2.2 Caesium

Until recently, few studies have focused on the effect of ¹³⁷Cs on the central nervous system of mammals. One report showed that the behavior (locomotion, short-term memory) of adult, healthy rats was not disrupted by chronic exposure to ¹³⁷Cs (6,500 Bq/L) in drinking water (Houpert et al. 2007). However, slight and transitory modifications of the sleep–wake cycle and of electro-encephalographic (EEG) activity were observed in these rats (Lestaev et al. 2006).

3.2.3 Non-radioactive Cadmium

Experimental studies on rats indicate that early exposure to cadmium can induce behavioral and neurotoxic effects, including a decrease of locomotor activity or an increase of anxiety-like behavior (Baranski 1984; Leret et al. 2003; Oskarsson et al. 1998). Cadmium exposure may also induce a general depression in rats (Ali et al. 1990).

3.3 Fish and Wildlife Species

3.3.1 Behavioral Measurements of Interest

Invertebrates are commonly used for the routine evaluation of the toxicity of chemicals. The behavioral endpoints that are measured include avoidance, feeding depression, valve closure and behavior, among others. If avoidance of contaminants occurs under natural conditions, then bioassays that require forced exposure prevent monitoring of the potential impairments from normal avoidance behavior. Properly conceived avoidance assays may therefore be needed to obtain cost-effective and ecologically relevant information on such behavior.

Chronic feeding assays offer a rapid, cheap and effective tool to garner useful biomonitoring results for contaminants in environmental species (Zhou et al. 2008). Various behavioral patterns of molluscs have been studied in such biomonitoring. In mussels, the periodicity of pumping activity and rest is a sensitive indicator of unfavourable conditions (Salanki et al. 2003). Valve-closure behavior is another useful toxicity endpoint, as has been shown for the Asiatic clam, *Corbicula fluminea*, exposed to cadmium (Tran et al. 2003). Earthworms are also commonly used in eco-toxicology studies, because of their burrowing habits and importance in soil habitat function. Avoidance and feeding behavior tests with earthworms have already been

implemented in uranium mines, and appear to be sensitive endpoints (Andre et al. 2009; Antunes et al. 2008).

Among vertebrates, fish are considered to be interesting and useful models for behavioral studies. Modifications of swimming behavior may alter the capacity of fish to feed, to avoid a predator or to reproduce. Therefore, swimming behavior in fish is a relevant sublethal indicator of toxicity (Little and Finger 1990). The zebrafish, *Danio rerio*, is considered to be a relevant neurobehavioral model because its nervous system is simpler than that of rodents, which allows the analysis of locomotor and memory capacities (Scalzo and Levin 2004). Simple locomotor behavioral effects are important endpoints when fish are studied, because locomotion is relatively easy to quantify with existing computerized imaging systems (Baatrup 2009); such systems allow the evaluation of locomotor activity, school preference or predator avoidance (Gerlai et al. 2000). Fast-start response (*i.e.*, response observed in the first seconds after a stimulus) has also been analysed in pollution-exposed zebrafish (Dlugos and Rabin 2003). Learning tests have recently been developed for use with zebrafish, and these tests are similar to ones used to evaluate learning in rodents and non-human primates (Carvan Iii et al. 2004; Levin and Chen 2004; Williams et al. 2002). Larger fish such as trout, sea bass and mullet are also commonly used as experimental models to study swimming behavior (Beauvais et al. 2000), feeding behavior (Millot et al. 2008), fast-start response (Lefrancois and Domenici 2006), exploration behavior (Millot et al. 2009) and swimming energetic performance (Lefrancois et al. 2007).

Studies have also been performed in contaminated areas to evaluate the effects of toxicants on migratory patterns and preferred nesting sites in birds (Moller and Mousseau 2006).

3.3.2 Uranium

Very few studies have addressed the effects of uranium on aquatic species. Of the studies that have been performed on such species, all were conducted on depleted uranium, which addresses only chemotoxicity, not radiotoxicity. Uranium exposure decreased valve opening time in the molluscs *Corbicula fluminea* (Fournier et al. 2004; Tran et al. 2005) and *Velesunio angasi* (Markich et al. 2000). Burrowing activity of the sludge worm, *Tubifex tubifex*, measured by the length of gallery network in sediment, was also reduced by uranium (Lagauzere et al. 2009). In zebrafish, uranium induced a decrease in fertility and altered courtship behavior (a qualitative measurement) (Bourrachot et al. submitted).

3.3.3 Caesium

In laboratory experiments, avian embryos irradiated with γ rays (2–10 Gy) showed no behavioral changes in post-hatching approach or colour preferences, when compared with controls; this suggests that the nervous system of bird embryos is less susceptible than that of the developing mammalian nervous system to the effects of

ionizing radiation (Oppenheim et al. 1970). Similarly, learning and memory abilities of exercised Japanese quails were not modified after single or repeated X-irradiation of the head (Konermann 1970).

Most knowledge on the effects of radioactive caesium on wildlife species comes from field studies performed in the Chernobyl-accident zone. Rodents from the Chernobyl zone, including the vole, *Microtus oeconomus*, showed higher vertical and horizontal locomotion compared to rodents from a less contaminated zone; in addition, the level of the vole's emotional reaction was lower (Karpenko et al. 2003). Radioactive contamination from Chernobyl also had negative effects on many bird species as shown both by their reduced species richness and abundance (Moller and Mousseau 2007b). These effects may result from a preference for nest sites in uncontaminated areas: one study showed that birds, including the great tit, *Parus major*, and the pied flycatcher, *Ficedula hypoleuca*, discriminated against breeding sites that had high radiation dose rates, thereby avoiding radioactively contaminated areas as reproduction sites (Moller and Mousseau 2007a). Furthermore, passerine birds like the barn swallow, *Hirundo rustica*, that breed in contaminated areas, had reduced hatching success and fecundity, and reduced survival prospects as a result of the Chernobyl accident (Moller et al. 2005). The abundance of birds of prey was also reduced in contaminated areas, and there is evidence of a recent increase in the abundance of raptors in less contaminated areas (Moller and Mousseau 2009). Therefore, populations that breed in radioactive sites seem to maintain population levels by immigration from elsewhere, rendering Chernobyl an ecological sink for such immigrants, as was demonstrated by the use of isotope dynamics technique in bird feathers (Moller et al. 2006).

3.3.4 Non-radioactive Cadmium

The effects of cadmium on environmental species are very well documented and several studies have addressed animal behavior endpoints after exposure to this pollutant.

Cadmium altered the feeding behavior of crustaceans after several days of exposure to low contaminant concentrations (6–60 µg/L); the exposed animals were freshwater decapods and amphipods and a terrestrial isopod (Felten et al. 2008; Pestana et al. 2007; Pynnonen 1996).

Molluscs and insects also demonstrated impairment of feeding behavior after cadmium exposure. Feeding rates were decreased from cadmium exposure levels of 0.1–0.5 mg/L in the freshwater snail, *Lymnaea peregra* (Crichton et al. 2004), the land snail, *Helix engaddensis* (Swaileh and Ezzughayyar 2000), and in the midge larvae, *Glyptotendipes pallens* (Heinis et al. 1990). The sandy shore scavenging gastropod, *Nassarius festivus*, showed a decrease in the number of animals feeding after exposure to 0.5 mg/L of cadmium, and the time spent feeding was increased (Cheung et al. 2002). Annelids seem to be more resistant to cadmium: the feeding behavior of three polychaetes was not modified by exposure to 40 mg/kg of cadmium in sediment (Olla et al. 1988). Cadmium also decreased filtration activity of the bivalves *Macoma balthica* (Duquesne et al. 2004) and *Potomida littoralis*

(Mouabad et al. 2001). Cadmium levels exceeding 2.0 mg/L decreased the time of valve opening in the Mediterranean mussel, *Mytilus galloprovincialis* (Ait Fdil et al. 2006).

Cadmium exposure may also alter organism mobility and burrowing activity. The swimming velocity of crustaceans, including the striped barnacle larvae, *Balanus amphitrite* (Lam et al. 2000), the shrimp *Hippolyte inermis* (Untersteiner et al. 2005), the amphipod *Gammarus pulex* (Felten et al. 2008) and the mysid *Neomysis integer* (Roast et al. 2001), was decreased in the presence of cadmium. In benthic animals, the presence of cadmium in sediment impaired the burrowing behavior, as was shown for the bivalves, *Macoma balthica* (McGreer 1979), *Cardium edule* (Amiard and Amiard-Triquet 1986) and the truncated wedgeshell, *Donax trunculus* (Neuberger-Cywiak et al. 2003), and the earthworm, *Lambito mauritii* (Sivakumar et al. 2003). However, cadmium had no effect on burrowing of polychaetes (Olla et al. 1988).

Cadmium potentially induces a displacement of terrestrial animals from their optimum environment. The isopod *Oniscus asellus* avoided cadmium-contaminated food pellets (Zidar et al. 2003). Cadmium also induced a transient avoidance in the whiteworm, *Enchytraeus albidus* (Amorim et al. 2008). Finally, in one study, it was demonstrated that the snail *Physella columbiana* has evolved to detect and avoid heavy metals, including cadmium, at mining sites (Lefcort et al. 2004).

Several authors have also shown the effects of cadmium on fish behavior. In adult zebrafish, high concentrations of cadmium induced a general lethargy (Grillitsch et al. 1999). Adult animals, continuously exposed to cadmium from the embryo stage, presented a decreased escape response to alarm substances, showing that cadmium could alter zebrafish neurogenesis and induce irreversible damage to adult behavior (Kusch et al. 2007). In the rainbow trout, *Oncorhynchus mykiss*, cadmium eliminated antipredatory behavior (Scott et al. 2003), although these animals could successfully escape from a cadmium-contaminated environment (Hansen et al. 1999b). Cadmium created several types of behavioral impairment in guppies: swimming in an imbalanced manner, capsizing, attaching themselves to the surface, difficulty in breathing and gathering around the ventilation filter (Yilmaz et al. 2004). The fast-start response of the sea bass, *Dicentrarchus labrax*, was also altered at 5 µg/L of cadmium exposure (Faucher et al. 2006). Cadmium also decreased exploration activity of the African snakehead, *Parachanna obscura* (Tawari-Fufeyin et al. 2007).

3.3.5 Cobalt Irradiation and Exposure

Sterile insect technique (SIT) is a pest control strategy that involves sterilizing males by exposing them to ionizing radiation, mostly using ^{60}Co . Under these conditions, the mating behavior of the Southern green stink bug, *Nezara viridula*, was not affected by irradiation at 5 Gy, but its fecundity was reduced (Zuniè et al. 2002). The mating behavior of the sweet potato weevil, *Cylas formicarius elegantulus*, also was unaffected during the first week of irradiation at 200 Gy, but was altered later (Kumano et al. 2008). In contrast, at an irradiation dose of 15 Gy impaired mating

behavior of the European spruce bark beetle, *Ips typographus*, occurred in males, but the burrowing behavior was only slightly modified (Turcani and Vakula 2007). Although the results and the doses are species-dependent, it can be concluded that irradiation does affect insect reproduction.

^{60}Co irradiation also alters reproduction in other species, such as the Kuruma shrimp, *Penaeus japonicus*, in which a decrease in maturation and spawning was shown in females (Sellars et al. 2007).

Fish are able to detect the presence of cobalt in the environment: rainbow trout, *Oncorhynchus mykiss*, and the Chinook salmon, *O. tshawytscha*, escaped from a contaminated area to an uncontaminated zone when cobalt reached levels of 180 and 24 $\mu\text{g/L}$, respectively (Hansen et al. 1999a).

4 Consequences

4.1 Consequences in Humans: Neurodegenerative Pathologies

The study of metal and radionuclide effects on neuronal physiology deserves specific attention, because of their consequences on locomotor and cognitive performances and their probable roles in the onset and/or progression of neurodegenerative diseases. Moreover, several neurological diseases (e.g., Alzheimer's and Parkinson's diseases) are characterized by the presence of intra- or extra-cellular deposits that contain proteins associated with metals. The aged people, infants and children are particularly sensitive to these pollutants. Any deficit or excess can alter cell fate or survival and lead to a neurodegenerative insult (Block and Calderon-Garciduenas 2009; Grandjean and Landrigan 2006). Therefore, the understanding of the pathophysiological roles played by metals and radionuclides in brain functions and properties is a public health issue. However, up to the present, the consequences of metals and radionuclides on brain functions and their molecular mechanism of action have been poorly understood.

4.2 Ecological Consequences

Behavioral alterations have biological (e.g., decreases of reproduction or survival) and ecological consequences (e.g., alteration of population structure or ecosystem functioning). Behavior is the link between physiological and ecological processes. Any degradation of the olfactory system in fish could affect migration and food-search behavior, ability to locate or detect spawning beds, and predator avoidance; such effects could lead to animal death and possibly to species extinction (Scott and Sloman 2004).

Ecological consequences may be reversible, if adaptive mechanisms are rapidly manifested. Ecological effects may also be irreversible, when exposure to toxics or irradiation exerts a selection pressure. Such a phenomenon is a basic hypothesis

of behavior ecotoxicology that derives from neo-Darwinian theory. Real (1994) suggests that ecological phenomena and community organization are immediate consequences of individual actions and behaviors.

However, the demonstration of a direct link between observed effects at the individual level (in laboratory experiments) and effects on natural communities is rarely done, mainly because of the complexity of natural ecosystems.

5 Conclusion and Future Work

Behavior is defined as the physical manifestation of the integrated physiological responses of an animal to its environment. Behavior can be a potentially excellent biomarker in some species for detecting environmental modification. Several neurochemical mechanisms modulate the adjustment of behavioral responses of organisms to environmental stimuli. The effects of metals on humans and animals (rodents, fish) have been relatively well described. However, data on the effects of radionuclides on humans and animals are missing or poorly represented. From our review, we conclude that the behavior of humans and other animals may be affected in marked ways by exposure to radionuclides. Some behavioral effects result from chemotoxicity of the underlying element, whereas others are caused by its radiotoxicity. The effects of radionuclide pollution on sensorial, locomotor or cognitive performance are variable and depend on several factors, including the element to which exposure takes place and its dose, the duration of the contamination, the species exposed and the type of the cerebral functions altered. We also conclude from our review that despite the fact that behavioral biomarkers can be very useful indicators for environmental damage, there are too few publications available to draw definitive conclusions for most radionuclides and species. Therefore, if the goal is to identify the most probable specific modes of action and damages caused by different radionuclides, further work is needed to improve our knowledge of the brain structures affected by different radionuclides.

6 Summary

Concomitant with the expansion of the nuclear industry, the concentrations of several pollutants, radioactive or otherwise, including uranium, caesium, cadmium and cobalt, have increased over the last few decades. These elemental pollutants do exist in the environment and are a threat to many organisms.

Behavior represents the integration of all the anatomical adaptations and physiological processes that occur within an organism. Compared to other biological endpoints, the effects of pollutants on animal behavior have been the focus of only a few studies. However, behavioral changes appear to be ideal for assessing the effects of pollutants on animal populations, because behavior links physiological functions with ecological processes. The alteration of behavioral responses can have severe implications for survival of individuals and of populations of

some species. Behavioral disruptions may derive from several underlying mechanisms: disruption of neuro-sensorial activity and of endocrines, or oxidative and metabolic disruptions. In this review, we presented an overview of the current literature in which the effects of radioactive pollutants on behavior in humans, rodents, fish and wildlife species are addressed. When possible, we have also indicated the potential underlying mechanisms of the behavioral alterations and parameters measured.

In brief, chronic uranium contamination is associated with behavior alterations and mental disorders in humans, and cognitive deficits in rats. Comparative studies on depleted and enriched uranium effects in rats showed that chemical and radiological activities of this metal induced negative effects on several behavioral parameters and also produced brain oxidative stress. Uranium exposure also modifies feeding behavior of bivalves and reproductive behavior of fish.

Studies of the effects of the Chernobyl accident shows that chronic irradiation to ¹³⁷Cs induces both nervous system diseases and mental disorders in humans leading to increased suicides, as well as modification of preferred nesting sites, reduced hatching success and fecundity in birds that live in the Chernobyl zone. No significant effect from caesium exposure was shown in laboratory experiments with rats, but few studies were conducted.

Data on radioactive cadmium are not available in the literature, but the effects of its metallic form have been well studied. Cadmium induces mental retardation and psychomotor alterations in exposed populations and increases anxiety in rats, leading to depression. Cadmium exposure also results in well-documented effects on feeding and burrowing behavior in several invertebrate species (crustaceans, gastropods, annelids, bivalves) and on different kinds of fish behavior (swimming activity, fast-start response, antipredatory behavior).

Cobalt induces memory deficits in humans and may be involved in Alzheimer's disease; gamma irradiation by cobalt also decreases fecundity and alters mating behavior in insects.

Collectively, data are lacking or are meagre on radionuclide pollutants, and a better knowledge of their actions on the cellular and molecular mechanisms that control animal behavior is needed.

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Illicit Drugs: Contaminants in the Environment and Utility in Forensic Epidemiology

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1 Introduction

The spectrum of chemicals recognized as contributing to widespread contamination of the environment was extended to pharmaceutical ingredients as early as the 1970s. The topic, however, did not begin to attract broader scientific attention until the mid-1990s (Daughton 2009a). Occurring generally at levels below 1 $\mu\text{g/L}$ (1 part per billion) in ambient waters, recognition of the near-ubiquitous presence of pharmaceuticals in a wide variety of environmental compartments serves as a stunning measure of the advancements in analytical chemistry and of our still-emerging understanding of the scope and complexity of xenobiotic occurrence in the environment.

More so than with any other class of environmental contaminants, drugs have served to illustrate the intimate, inseparable, and immediate connections between the actions, activities, and behaviors of individual citizens and the environment in which they live (Daughton 2001a). Drug contaminants also highlight the profound changes that have occurred in how risk is perceived by the public. After all, it has now been 40 years since the occurrence of an emblematic event that was a major catalyst for the creation of the US EPA (in 1971) and which was followed soon after by the Federal Water Pollution Control Amendments of 1972 and the Clean Water Act of 1977 and later by the Water Quality Act of 1987. This event was the 1969 Ohio Cuyahoga River fire, which otherwise had little broad environmental significance because more than a dozen similar fires had occurred in the preceding 100 years (with the largest occurring in 1952), all resulting from the river's continual accumulation of combustible floating debris and petroleum wastes.

Gross-level pollution of waterways had not been confined to the Cuyahoga River. But, the 1969 fire was a landmark event and changed the way the environment was viewed. The extent of progress and effectiveness of pollution regulation, mitigation, control, and prevention over the last 40 years is now reflected by a focus on trace-level chemical pollutants – an evolutionary change not contemplated in the early 1970s but made possible by continual advancements in instrumental analytical chemistry that began in the 1960s. This focus is embodied particularly with the so-called emerging contaminants (Daughton 2009b) and the myriad others not yet noticed or identified, which could be referred to as the “quiet contaminants.”

Until the mid-2000s, the emerging study of pharmaceuticals in the environment (PiE) inexplicably excluded from consideration one major aspect – the contributions to overall environmental loadings by the so-called illicit drugs. A structurally

diverse group of chemical agents uniformly possessing extremely high potential for biological effects in humans and non-target organisms alike, illicit drugs are used in enormous quantities worldwide. However, the actual magnitude of illicit drugs is unknown and can only be roughly estimated. The potential for illicit drugs to enter the environment via a wide array of pathways should not differ much from that of pharmaceuticals used in the practice of medicine. Although it had been known for many decades that illicit drugs and their metabolites (just as with pharmaceuticals used in the practice of medicine) are excreted in urine, feces, hair, and sweat, the ramifications for the environment were basically ignored until 1999 (Daughton and Ternes 1999) and 2001 (Daughton 2001a, c), when the scope of concerns surrounding PiE was expanded to include illicit drugs. In characterizing and assessing risks incurred from PiE, both licit and illicit drugs need to be considered seamlessly.

Perhaps the first published indication that illicit drugs might be pervasive contaminants of our immediate surroundings and the environment was a 1987 FBI study performed in response to a newspaper report 2 years earlier that cocaine was present on money in general circulation (Aaron and Lewis 1987). Over the intervening 20 years, analogous surveys of illicit drug ambient contaminants have been attempted for the first time for sewage wastewaters (Khan 2002), surface waters (Zuccato et al. 2005), air (Cecinato and Balducci 2007), sewage sludge (Kaleta et al. 2006), biosolids (Jones-Lepp and Stevens 2007), and most recently drinking water (Huerta-Fontela et al. 2008a). An examination of the US EPA's bibliographic database on pharmaceuticals in the environment (USEPA 2009b) shows that the core journal references having a major focus on illicit drugs in wastewaters, ambient waters, drinking water, or the air total about 70 (excluding those published on the topic of drugs on money). The number of references (in any type of technical publication) dealing with illicit drugs in the environment is fewer than 200; this number comprises only 2% of the roughly 10,000 documents that address the general topic of PiE.

Presented herein is the first broad overview of the topic of illicit drugs as environmental contaminants. Summary perspectives are provided of the published data on their occurrence in a spectrum of environmental compartments, what their occurrence might mean with regard to risk, and an historic perspective on how their occurrence can be used as an analytical measurement tool to assess society-wide usage of illicit drugs. An illustrated flowchart depicting the varied routes by which illicit drugs gain entry to our immediate surroundings and to the ambient environment is presented in Fig. 1.

The chronology of seminal publications that address the significant aspects of illicit drugs and the environment is presented in Table 1. The topic is transdisciplinary, involving the knowledge from a variety of disparate but intersecting fields, including health care, pharmacology, criminology, forensic sciences, epidemiology, toxicology, environmental and analytical chemistry, and sanitary engineering.

This chapter builds upon previous work, which is scheduled to be published in one of the only books to date devoted to the topic of illicit drugs in the environment (Daughton 2011 – in press).

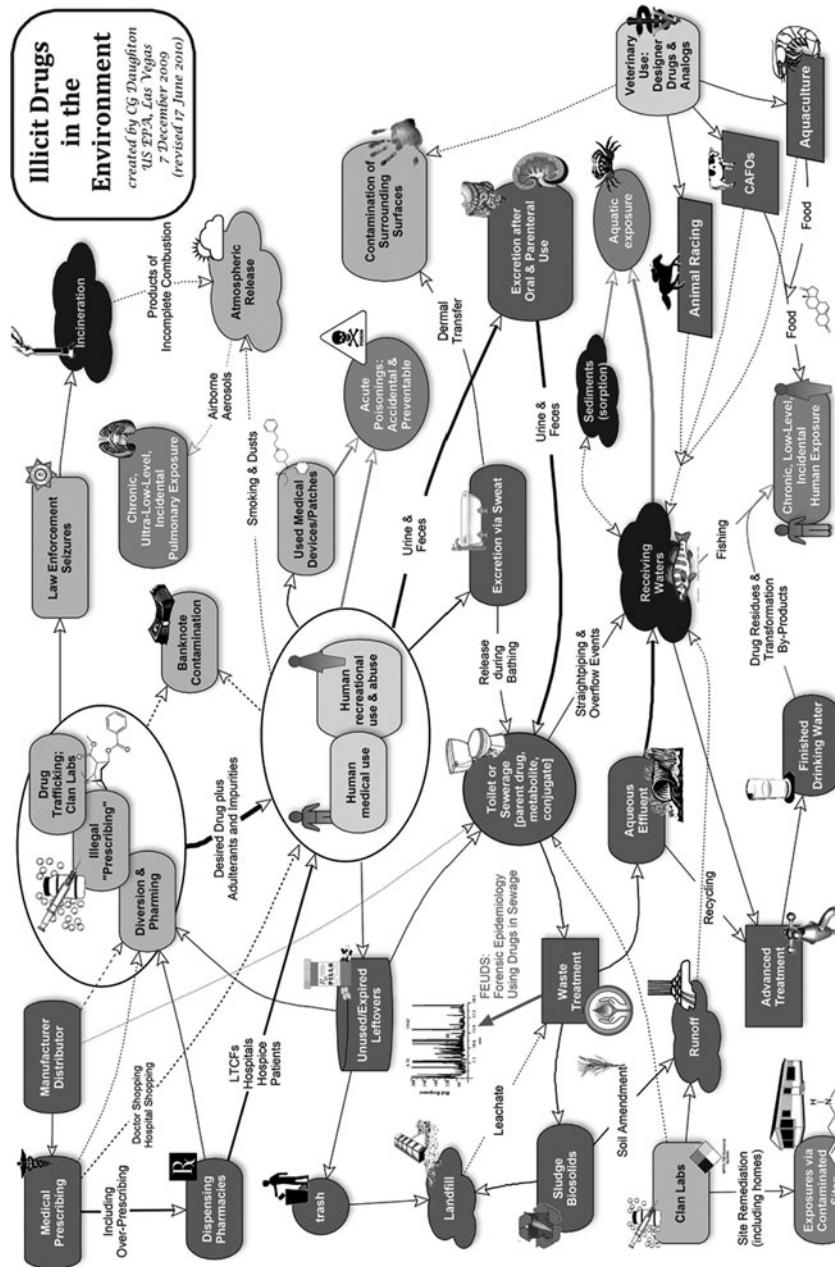


Fig. 1 Illicit drugs in the environment (relative significance of routes indicated by intensity of lines)

Table 1 Chronology of some selected seminal publications regarding illicit drugs in the environment

Year	Aspect	Unique features of study	References
1987	M	<i>First report in a journal confirming the presence of an illicit drug (cocaine) on banknotes in general circulation</i> (objective to distinguish 'drug' money from "innocent" money)	Aaron and Lewis (1987)
1998	A	Perhaps <i>first data on an illicit drug in the ambient environment; non-target analysis revealed cocaine associated with fractions of particulate matter in outdoor air</i> (Los Angeles)	Hannigan et al. (1998)
2000	M	<i>First comprehensive overview of drugs on banknotes</i>	Sleeman et al. (2000)
2001	F	<i>Use of residues in sewage to reconstruct community-wide drug usage</i> <i>first proposed</i> (later to be termed "sewage epidemiology" or "sewage forensics," or sometimes "community drug testing" or "community urinalysis"); <i>first discussion to broaden the topic of drugs as environmental contaminants to include illicit drugs</i>	Daughton (2001c)
2002	WW	Morphine, methamphetamine, and methadone in sewage	Khan (2002)
2004	WW, monit	Methamphetamine and MDMA (3,4-methylenedioxymethamphetamine) in WWTP (Wastewater Treatment Plant) effluent; first report by US EPA of illicit drug in the environment; <i>first use of integrative time-weighted sampling for illicit drugs in wastewaters</i>	Jones-Lepp et al. (2004)
2004	M	THC ($\Delta 9$ -tetrahydrocannabinol), cannabinol, and cannabidiol on banknotes from the USA and other countries	Lavins et al. (2004)
2005	WW	Morphine and methamphetamine is sewage sludge and WWTP influent; methadone and morphine in aqueous phase of digested sludge	Khan and Ongjerth (2005)
2005	WW	<i>First report of widespread occurrence of an illicit drug in surface water and wastewater</i> (cocaine and BZE – benzoyllegomine – in WWTP influent and river)	Zuccato et al. (2005)
2005	F	<i>First implementation of "sewage epidemiology" to reconstruct community-wide drug usage</i>	Zuccato et al. (2005)
2005	M	Diacetylmorphine on banknotes	Ebejer et al. (2005)

Table 1 (continued)

Year	Aspect	Unique features of study	References
2006	WW	<i>First study to target a spectrum of illicit drugs and metabolites in WWTP influents and effluents</i> ; those not identified in prior studies: norbenzoyllegonine, norcocaine, cocaethylene, 6-acetylmorphine, morphine-3-D-glucuronide, amphetamine, MDA (3,4-methylenedioxymethamphetamine), MDMA (3,4-methylenediox-N-ethylamphetamine), EDDP (2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine), 11-nor-9-carboxy-9'-THC Codeine, dihydrocodeine, hydrocodone, oxycodone, tramadol in WWTP influents and effluents, and surface water	Castiglioni et al. (2006)
2006	WW	<i>First report in peer-reviewed literature of an illicit drug in sewage sludge</i> (amphetamine in sewage sludge)	Hummel et al. (2006)
2006	SS	<i>First nationwide monitoring in the USA of illicit drugs in sewage</i> ; study by the Office of National Drug Control Policy (ONDCP) targeted about 100 WWTPs across two dozen regions in the USA (results never published)	Kaleta et al. (2006)
2006	F, monit	<i>First multi-country monitoring of cocaine in wastewater to estimate usage</i> <i>First targeted analysis of ambient air for an illicit drug</i> ; cocaine quantified in particulates from all air sampled around Rome and several other Mediterranean locations (also in air samples archived several years prior)	See Bohannon (2007)
2006	F	<i>First multi-country monitoring of cocaine in wastewater to estimate usage</i>	See UNODC June (2007)
2007	A	<i>First targeted analysis of ambient air for an illicit drug</i> ; cocaine quantified in particulates from all air sampled around Rome and several other Mediterranean locations (also in air samples archived several years prior)	Cecinato and Baldacci (2007)
2007	SS	<i>First report of an illicit drug in biosolids</i> (methamphetamine in sewage biosolids)	Jones-Lepp and Stevens (2007)
2007	WW	Norcocaine, THC, THC-COOH in WWTP influents and effluents and surface water	Boleda et al. (2007)
2007	M	BZE and heroin on banknotes	Bones et al. (2007b)
2007	R	<i>First conference devoted to topic of illicit drugs in the environment; led to first published overview of many of the aspects of the topic</i> (including scientific, technical, social, privacy, ethical, and legal concerns)	EMCDDA (2007), Frost and Griffiths (2008)
2008	DW	<i>First data on the occurrence and stepwise removal of illicit drugs at a municipal drinking water treatment plant</i>	Huerta-Fontela et al. (2008a)
2008	WW	Methadone, EDDP, and cocaethylene in surface waters	Zuccato et al. (2008b)

Table 1 (continued)

Year	Aspect	Unique features of study	References
2008	WW	Cocaethylene, LSD (and nor-LSD and 2-oxo-3-hydroxy-LSD), heroin, Δ^9 -THC (and 11-hydroxy-THC and nor-THC), (R,R)(-)-pseudoephedrine and (1S,2R)(+)-ephedrine hydrochloride in WWTP influents and effluents	Postigo et al. (2008b)
2008	F, monit	Weekly temporal wastewater fluctuations in various drug classes	Zuccato et al. (2008a)
2008	F	<i>First use of the term “sewage epidemiology” in peer-reviewed literature; perhaps first mentioned in a 2007 interview by Fanelli (Bohannon 2007)</i>	Zuccato et al. (2008a)
2008	F	<i>Creatinine in urine first assessed as means of normalizing drug concentrations across WWPs (and therefore to facilitate drug usage comparisons across communities); creatinine first analyzed in sewage. Creatinine first proposed as a means for normalizing data by Daughton (2001c)</i>	Chiaia et al. (2008)
2008	WW, monit	First systematic survey of illicit drugs in surface waters	Zuccato et al. (2008b)
2008	M, R	<i>First overview of an illicit drug (cocaine) from banknotes from multiple countries</i>	Armenta and de la Guardia (2008)
2008–2009	R	<i>First major overviews of illicit drugs in the environment</i>	Kasprzyk-Hordern et al. (2009a), Postigo et al. (2008a), Zuccato and Castiglioni (2009), Zuccato et al. (2008a)
2008–2009	R, M	<i>First major overviews of the analytical approaches used for illicit drugs in the environment</i>	Castiglioni et al. (2008), Zuccato and Castiglioni (2009)
2008–2009	EF	<i>First major overviews of the analytical approaches used for illicit drugs on money</i>	Armenta and de la Guardia (2008)
2009	DW	<i>First studies regarding the sorption of illicit drugs to sediments, soils, and sewage sludge</i>	Barron et al. (2009), Stein et al. (2008), Wick et al. (2009)
2009	R	<i>First data on the occurrence and stepwise removal of cannabinoids at a municipal drinking water treatment plant</i>	Boleda et al. (2009)
2009	WW	<i>First major overview of illicit drugs in airborne particulates</i> Egonine methyl ester (EME) in WWTP influents; EME possibly in surface water	Postigo et al. (2009) van Nuijs et al. (2009a), Vazquez-Roig et al. (2010)

Table 1 (continued)

Year	Aspect	Unique features of study	References
2009	WW	<i>First time that illicit drugs (cocaine, BZE, and morphine) monitored monthly in the sewage from an entire city over the course of a year</i>	Mari et al. (2009)
2009	sw	<i>Sweat first proposed as a means of general transfer of drugs not just to sewage (via bathing and laundry) but also to any object in the surrounding environment contacted by skin (dermal transfer)</i>	Daughton and Ruhoy (2009)
2009	monit	<i>First geographic spatial surveys; 24-h composite WWTP influent samples representing 65% of population of State of Oregon analyzed for BZE, methamphetamine, and MDMA, and Belgium-wide survey of cocaine, BZE, and ecgonine methylester</i>	Banta-Green et al. (2009), van Nuijs et al. (2009b, c)
2009	A	<i>First qualitative report of cannabinoids in ambient air aerosols (in Rome)</i>	Cecinato et al. (2009b)
2009	A	$\Delta 9$ -Tetrahydrocannabinol, cannabidiol, and cannabinol identified in ambient air particulates	Baldacci et al. (2009)
2009	A, monit	<i>First quantitative study of cocaine in ambient air across several continents</i>	Cecinato et al. (2009a)
2009	WW	Cannabinoids in surface waters	Boleda et al. (2009)
2010	WW	nor-LSD, O-H-LSD, THC-COOH, OH-THC identified in surface waters (river)	Postigo et al. (2010)
2010	A	<i>First use of existing air quality monitoring sites for detection of multiple drugs of abuse, including amphetamines, cannabinoids, cocaine, lysergics, and opioids (Spain)</i>	Viana et al. (2010)
2010	WW	<i>First enantiomeric speciation analysis of illicit drugs in wastewater; including amphetamines, ephedrines, and venlafaxine</i>	Kasprzyk-Hordern et al. (2010)
2010	WW	<i>First identification of buprenorphine in sewage, with concentrations ranging up to 20 ng/L in WWTP influents (France)</i>	Karolak et al. (2010)
2010	WW	<i>First survey of wastewater from US pharmaceutical manufacturing facilities reveals relatively high levels (sub-nug/L) of a range of drugs of abuse: butalbital, carisoprodol, methadone, and oxycodone</i>	Phillips et al. (2010)
2010	WW	<i>Comprehensive review of FEUDS</i>	van Nuijs et al. (2010 – in press)

A=air; DW=drinking water; EF=environmental fate; F=forensics; M=money (banknotes); monit=monitoring; R=review; SS=sewage sludge (and biosolids); sw=sweat; WW=wastewater

2 What Is an “Illicit” Drug?

Any discussion regarding illicit drugs can become confused by the ambiguity as to what exactly defines an illicit drug. Confusion stems from the fact that illicit drugs are not limited exclusively to illegal drugs – that is, drugs with no medical use. Illicit drugs can include active ingredients from bona fide registered pharmaceuticals having valuable therapeutic uses – two common examples being morphine and oxycodone. They can also include active ingredients that are banned from all use under various international conventions or national law, as they are deemed as having no use in health care. Whether a drug is illicit (or illegal) can be dictated by a number of different characteristics, including the chemical structure of the active ingredient or the way in which the drug is manufactured, formulated, labeled, distributed, acquired, or used. Some further discussion is presented below to better describe the circumstances under which a drug is considered “illicit.”

2.1 Terminology

There is no single, widely used term that accurately captures the myriad numbers of substances that become abused by habitual or addictive use. The term “illicit drug,” while widely used, is not accurate in the sense that most of the widely known abused drugs have bona fide medical uses as licit pharmaceuticals; the few that do not are incorporated in the listings of controlled substances maintained by various countries, such as Schedule I in the USA.

A variety of terms are loosely used – often interchangeably – in discussions regarding illicit drugs. Major terms include street drugs, designer drugs, club drugs, drugs of abuse, recreational drugs, clandestinely produced drugs, and hard and soft drugs. The term “research chemicals” had been used by the clandestine laboratory community as an alternative term for designer drugs – with the original intent being that the chemicals were for legitimate research purposes rather than human use (and therefore not subject to regulation); more recently, however, the manufacture of drug analogs as “research chemicals” has become a gray area of the law and is the bona fide trade of those commercial laboratories synthesizing them for biomedical research. The term “designer” drug was first applied in the 1980s to various analogs of fentanyl and then gained popularity when 3,4-methylenedioxymethamphetamine (MDMA, ecstasy) was introduced to the black market; but, perhaps the most notable first “designer” drugs were introduced in the 1920s (i.e., dibenzoylmorphine and acetylpropionylmorphine). A short history of designer drugs is presented by Freye (2009).

Rather surprisingly, no single illicit drug term exists for capturing the full scope of intended meaning. Regardless of the terminology, much overlap exists with licit pharmaceuticals (those with approved medical uses). This can lead to much confusion or ambiguity as to exactly what the scope of the topic is. The confusion surrounding illicit drug terminology is discussed in papers authored by Sussman and Huver (2006) and Sussman and Ames (2008).

In the overview provided herein regarding the environmental aspects of illicit drugs, the guiding definition used is that of the United Nations Office on Drugs and Crime (UNODC), which focuses not on the chemical identity of the drug itself, but rather on the life cycle pathway traveled by a drug. The UNODC does not recognize any distinction between the chemical identity of licit and illicit drugs – only the way in which they are used (UNODC 2009b). In this sense, the term “illicit” refers to the way in which these drugs are manufactured, formulated, distributed, acquired, and consumed and by the fact that they are being used for non-medical purposes – that is, obtaining drugs without a bona fide prescription and using them in the absence of medical supervision.

This definition allows the inclusion of legal pharmaceuticals – that is, when they are manufactured, formulated, distributed, trafficked, or used illegally or diverted from legal sources. For those illicit drugs that originate from diversion of legitimate pharmaceuticals, the many sources and the means for their control to reduce their entry to the environment have been discussed by Ruhoy and Daughton (2008). For those that have illegal origins, the sources and routes to the environment are illustrated in Fig. 1. The wide spectrum of sources, and the routes by which legal drugs become diverted for illicit use, range from the relatively large-scale diversion from pharmaceutical manufacturers, distributors, pharmacies, and health-care facilities to the smaller scale (e.g., “theft” from home storage locations for teen “pharming”) and reuse of used medical devices, especially transdermal medical patches, which present lethal hazards for both intentional and accidental exposures (Daughton and Ruhoy 2009).

A closely allied aspect of illegal drugs is counterfeiting. Counterfeiting may involve the repackaging of medical pharmaceuticals that have been either diverted from legitimate sources or manufactured illegally, or the substitution of the advertised ingredient with other substances. Counterfeit is therefore not necessarily synonymous with “fake.” Counterfeiting can involve the addition of adulterants to the legitimate pharmaceutical, substitution with less-costly but illegally acquired active pharmaceutical ingredients, or substitution with potentially toxic non-pharmacologic substances. Counterfeit drugs are recognized as a significant threat to human health as a result of the presence of an undeclared active ingredient, excessive dose of a declared ingredient, or absence of a declared active ingredient (WHO 2008). Counterfeiting results in the entry of drugs to legal and illegal distribution channels; drugs can pretend to be either illicit or legitimate. The actual scope of counterfeiting worldwide is not known, but available data indicate it to be enormous and escalating. Of the pharmaceuticals in the developed world, one estimate is that 1% are counterfeit, and in the developing world 10–50% may be counterfeit (Everts 2010). Although counterfeiting often produces drug ingredients that are illegal, it is excluded from the scope of the discussion here.

The scope of this discussion also includes all other chemicals associated with the illegal manufacture (including reformulation of diverted pharmaceuticals) or trafficking of drugs, such as adulterants and impurities (Table 2). With these distinctions acknowledged, the following discussion will tacitly use a variety of terms very loosely. When the term “pharmaceutical” is used, the intention is to reference

Table 2 Adulterants and impurities in illicit drugs (a very small sampling)

Cocaine	MDMA (ecstasy: 3,4-methylenedioxymethamphetamine)
α - and β -truxillines (probably photodimers of cinnamoyl cocaine)	1-(3,4-Methylenedioxy)phenylpropanol-2
3,4,5-Trimethoxycocaine	1-(1,2-Dimethyl-1-azacyclopropyl)methyl-3,4-methylenedioxobenzene
Benzoyl pseudotropine	1,2-(Methylenedioxy)-4-methylbenzene
Benzoyltropine	1,2-(Methylenedioxy)-4-(2-N-methyliminopropyl)benzene
<i>cis</i> - and <i>trans</i> -Cinnamoyl ecgonine (hydrolysis of <i>cis</i> - and <i>trans</i> -cinnamoyl cocaine)	1,2-(Methylenedioxy)-4-propylbenzene
<i>cis</i> - and <i>trans</i> -Cinnamoyl cocaine (aka methylecgonine cinnamate) (up to 5% by weight)	1,2-Dimethoxy-4-propenylbenzene 3,4-Methylenedioxophenyl-2-propanol (MDP) 3,4-Methylenedioxo-phenyl-2-propanone (MDP2P)
Cuscohygrine (pyrrolidine alkaloid in coca)	3,4-Methylenedioxymphetamine (MDA)
Diastereomers of synthetic cocaine (pseudococaine, allococaine, allopseudococaine, D-enantiomer of cocaine)	3,4-Methylenedioxo-N-methylbenzylamine (MDB)
Diltiazem (adulterant)	3,4-(Methylenedioxy)benzaldehyde
Egonine methyl ester (hydrolysis of cocaine)	4-Methoxy-N-dimethyl-benzeneethanamine
Egonine (hydrolysis of cocaine)	4-Methyl-5-phenyl pyrimidine
Hydroxytropacocaine	Dextromethorphan (adulterant)
Methylecgonine	Dimenhydrinate (adulterant)
<i>N</i> -formyl-cocaine	Isosafrole
Norcocaine	Safrole
Tropocaine	<i>N</i> -formyl-3,4-methylenedioxymethamphetamine (<i>N</i> -formyl-MDMA)
Phenacetin (up to 50% by weight) (adulterant)	<i>N</i> -formyl-amphetamine
Xylazine (adulterant)	<i>N</i> -formyl-methamphetamine
Hydroxyzine (adulterant)	<i>N</i> -ethyl-3,4-MDA (MDEA)
Hygrine (pyrrolidine alkaloid in coca)	<i>N,N</i> -dimethyl-MDA
Levamisole (up to 4% by weight) (adulterant)	<i>N</i> -ethyl- <i>N</i> -methyl-1,2-methylenedioxy)-4-(2-aminopropyl)benzene
Lidocaine (adulterant)	<i>N,N</i> -dimethyl-(1,2-methylenedioxy)-4-(2-aminopropyl)benzene
	Piperonal
Methamphetamine	Heroin
1-Benzyl-3-methylnaphthalene	(Z)- <i>N</i> -acetylhydronorcarceine
1,2-Dimethyl-3-phenylaziridine	6-Acetylmorphine
1,3-Dimethyl-2-phenylnaphthalene	3-O,6-O,N-triacetyl morphine
3,4-Dimethyl-5-phenyloxazolidine	3,6-Dimethoxy-4,5-epoxyphenanthrene
<i>cis</i> -1,2-Dimethyl-3-phenylaziridine	4-O-acetylthebaol
<i>cis</i> -3,4-Dimethyl-5-phenyl-2-oxazolidone	4,6-Diacetox-3-methoxyphenanthrene
Dimethyl amphetamine	4-O-Thebaol
Dimethylsulfone (adulterant)	6-O,N-Diacetyl norcodeine
<i>N</i> -benzyl amphetamine	(E)- <i>N</i> -acetylhydronorcarceine
<i>N</i> -acetyl methamphetamine	Acetylcodeine
<i>N</i> -methyl ephedrine	Meconine
<i>N</i> -methyl pseudoephedrine	Clenbuterol (adulterant)
<i>N</i> -ethyl methamphetamine	<i>N</i> -acetyl norlaudanosine

Table 2 (continued)

Methamphetamine	Heroin
<i>N</i> -formyl amphetamine	<i>N</i> -acetylornnarcotine
<i>N</i> -acetyl ephedrine	Noscapine (up to 60% by weight)
<i>N</i> -ethyl amphetamine	Papaverine (up to 20% by weight)
<i>N</i> -formyl methamphetamine	1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine
<i>N,N</i> -dimethyl amphetamine	(MPTP) [during synthesis of
<i>p</i> -Bromotoluene	1-methyl-4-propionoxypyridine (MPPP), an
Phenyl-2-propanone (P2P)	analog of meperidine]

the active ingredients legally registered for use in drugs consumed for approved medical use under formal medical supervision.

What constitutes an illicit drug is a complicated function of social mores and evidence-based health studies, which are sometimes at odds with one another. These conflicts and inconsistencies are reflected, for example, in the opinions expressed by Nutt (2009), which have served to catalyze increasing scrutiny and debate. Illicit substances (drugs and the precursors used for their manufacture) are captured on various government lists (controlled substance *schedules*) that attempt to control and limit their use. The primary criteria justifying inclusion on such lists are health risks, potential for abuse/addiction (partly based on actual data), therapeutic value, and utility as precursors for illicit manufacturing. The unifying worldwide scheme, used by the EU, for regulation of illicit substances comprises the Schedules of the three UN Conventions of 1961 (United Nations Single Convention on Narcotic Drugs, New York, amended 1972), 1971 (Convention on Psychotropic Substances, Vienna), and 1988 (Convention Against Illicit Traffic in Narcotic Drugs and Psychotropic Substances, introducing control on precursors, Vienna). Combined, these Schedules currently comprise about 250 explicitly named controlled substances, according to the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA 2009b).

The lines of demarcation between licit and illicit drugs have become blurred. To illustrate, prescription analgesic opioids (which are controlled prescription drugs; CPDs) have now superseded heroin and cocaine in the USA in leading to fatal drug overdoses (Paulozzi and Xi 2008). Indeed, the use of certain licit drugs, including over-the-counter (OTC) medications, for non-medical purposes has recently surpassed the use of illicit drugs (NIDA 2008). For example, of the top 10 drugs that are misused by high-school seniors in the USA, 7 were legal prescription or OTC medications. Emergency room visits resulting from prescription opioid analgesics more than doubled from 2004 to 2008 and were highest for oxycodone, hydrocodone, and methadone (Cai et al. 2010).

Numerous other illicit substances (such as structural analogs) exist but can only be captured implicitly by generalized chemical criteria that preemptively ban their synthesis; not all countries, however, implicitly capture chemical analogs in their regulations. For example, the US Analogue Act (21 U.S.C. § 813: <http://www.justice.gov/dea/pubs/csa/813.htm>) is a section of the US Controlled

Substances Act that specifies “A controlled substance analogue shall, to the extent intended for human consumption, be treated, for the purposes of any Federal law as a controlled substance in schedule I.” Many additional substances are produced or used illicitly, but their chemical identities are elucidated only after they have experienced sufficient illegal use (often, once adverse medical problems in the general population are documented). A central reference that provides the chemical structures for many of these substances (those listed by the Canadian Controlled Drugs and Substances Act) is maintained on a web page by Chapman (2009).

Further confusion is added to the distinctions between illicit drugs and medical pharmaceuticals because the laws dealing with illicit drugs vary dramatically from country to country. Long-standing drug policies in certain countries are also in a state of flux, as various changes are being considered or are underway. Such changes range from “reducing harm” (e.g., via decriminalization of possession and use) to acknowledgment from the American Medical Association regarding the medical benefits of a Schedule I drug (i.e., namely cannabis) and calling for its clinical research (AMA 2009). Since Portugal began decriminalizing drug use, possession, and acquisition by drug end-users in 2001 (Law no. 30/2000, which focuses on harm reduction) (Greenwald 2009), the spectrum of laws dealing with illicit drugs has diversified; but, growing, illegal manufacturing, and trafficking remain criminal offenses. Among the EU States, the spectrum of law is captured by EMCDDA (2009a). The approaches and evidence used for classifying drugs as illicit are under increasing evidence-based scrutiny and debate (e.g., see Nutt 2009).

2.2 Differences Between Illicit and Licit Drugs as Environmental Contaminants

The primary factor distinguishing illegal from licit (registered) drugs is that the former have no legal (registered) uses, whereas the latter may experience illegal usage. With respect to understanding their overall significance in the environment, seven aspects of illicit drug use contrast sharply with legitimate pharmaceutical use:

- (1) For most illicit drugs, there are no accurate quantitative data available on their production or usage. For regulated pharmaceuticals, sales figures and regional real-time prescription data can be used in models to calculate predicted environmental concentrations (PECs); these values can then be compared with measured environmental concentrations (MECs).
- (2) Although the chemical identities for the core group of illicit drugs are known, an ever-increasing number of new drugs (such as structural analogs with minor modifications of regulated pharmaceuticals and of previously known illicit drugs – so-called designer drugs or clandestinely produced drugs) can elude detection by forensics laboratories for years before they are noticed and identified. The myriad numbers of designer drugs and constant synthesis of new ones

will pose challenges for mass spectrometrists in the coming years and introduces great uncertainty to the true scope of synthetic chemicals that actually contaminate the environment; for example, see the Psychonaut Web Mapping Research Group (2010) and EMCDDA (2010). Although many of these unique chemicals are probably produced in relatively small quantities, the fact that they belong to relatively few chemical classes may mean that they share relatively few mechanisms of biological action (MOAs). This increases the probability of biological effects resulting from dose (or concentration) “additivity.” When multiple chemical toxicants in a mixture share the same MOA, the dose or concentration of each toxicant can add to that of the others. Even if the concentration of each individual toxicant is below an effect threshold, the mixture’s combined dose can elicit effects as if it constitutes a single larger dose – a phenomenon informally referred to as “something from nothing” (Kortenkamp et al. 2009). Dose additivity is distinct from potentiation, where a chemical having no biological action of its own can enhance the action of another. Some designer drugs are highly potent, having extremely low effective doses (e.g., in the range of 1 µg per human use), and this has environmental implications, especially for aquatic exposure. As examples, cis-3-methylfentanyl and β-hydroxy-3-methylfentanyl (as with carfentanyl, a large animal tranquilizer) are extraordinarily potent designer drugs – being 3–5 orders of magnitude more potent than morphine.

- (3) Drugs manufactured via illicit routes are commonly contaminated with unintended impurities and purposeful adulterants (Table 2). These are often present at extremely high levels (e.g., sometimes more than half of the total mass, as opposed to mg/kg [ppm] levels for impurities in registered medicines) and are often more toxic than the sought-after drug ingredient.
- (4) The manufacture of illicit drugs (particularly methamphetamine) can cause extensive ecological damage as well as irreversible damage to infrastructure such as buildings (Cohen et al. 2007; Snell 2001; USEPA 2009a).
- (5) The primary interest in residues of illicit drugs in the environment has not been their occurrence in the environment as contaminants, but rather their presence in sewage (mainly untreated raw sewage) for use as a tracking tool to calculate levels of their community-wide consumption. This relatively new tool has been termed *sewage (or sewer) forensics (or epidemiology)*, but later in this chapter is referred to as FEUDS: “Forensic Epidemiology Using Drugs in Sewage.” In contrast to the licit use of pharmaceuticals, interest in the potential for illicit drugs as biological stressors in the environment has been secondary, and very little is known.
- (6) Compared with pharmaceuticals, much less is known about the toxicology (including pharmacokinetics), especially in the aquatic environment, of many illicit drugs (particularly designer drugs); for human research, there are added legal and ethical difficulties in performing studies on them. Knowledge of the scope of bioactive metabolites and extent of reversible conjugation is comparatively limited.

(7) Numerous measures are routinely implemented to reduce the entry of licit pharmaceuticals into the environment and moderate their potential for adverse effects. Routes of entry span an enormous spectrum of possibilities (Daughton and Ruhoy 2008). With illicit drugs, pollution prevention measures are straightforward but more difficult to implement – namely, discourage their manufacture, distribution (e.g., via unapproved “rogue” Internet pharmacies), and end use (Fig. 1).

The rate of introduction of new pharmaceuticals with potential for abuse and of new illicit substances precludes any comprehensive definitive worldwide compilation of such chemicals. The INCB (International Narcotics Control Board) maintains three major listings (INCB 2009): Yellow List (Narcotic Drugs under International Control), Green List (Psychotropic Substances under International Control), and Red List (Precursors and Chemicals Frequently Used in the Illicit Manufacture of Narcotic Drugs and Psychotropic Substances under International Control). A convenient listing of many of the corresponding chemical structures is provided by Chapman (2009).

3 The Core Illicit Drugs and the Environment

The types of drugs commonly abused are categorized in various ways, depending on their origin and biological effect. They can either be naturally occurring, semi-synthetic (chemical manipulations, such as analogs, of substances extracted from natural materials), or synthetic (created entirely by laboratory synthesis and manipulation). The primary categories are opiates, other CNS depressants (sedative-hypnotics), CNS stimulants, hallucinogens, and cannabinoids.

The scope of chemicals that could be considered illicit can be viewed in terms of the following categories of medical efficacy:

- (1) no known medical use (which are illegal in all circumstances according to various conventions) (e.g., benzylpiperazine; or heroin in the USA),
- (2) limited established medical use but also manufactured illegally and used primarily for non-medical purposes (e.g., methamphetamine),
- (3) firmly established with wide medical use but diverted for illegal use (e.g., theft; illegal prescription such as via unapproved Internet “pharmacies”),
- (4) firmly established wide medical use and legally obtained, but for non-medical use (e.g., doctor/hospital shopping or by other con schemes),
- (5) biological action similar to prescription drugs but synthesized as analogs, which are not individually and explicitly categorized as illegal; examples include the numerous analogs of phosphodiesterase (PDE) type-5 inhibitors.

All of these categories tend to primarily comprise drugs with high potential for abuse or recreational use.

Residues of some drugs in the environment have substantial multiple origins (both legal and illegal) making it difficult to ascribe or apportion monitored levels to illicit use. Morphine is one example. Morphine residues can originate from medical use of morphine itself or from codeine (via *O*-demethylation). It can also originate from diverted morphine or codeine as well as from heroin. By collecting data on other (and more unique) metabolites, these pathways can be teased apart. Using morphine as an example, by monitoring for the heroin metabolite 6-AM (6-acetylmorphine), a more reliable idea can be obtained to ascribe what portion of morphine originates from heroin usage.

While drug usage patterns and prevalence vary among countries and with time, those drugs in frequent use in the USA can serve as an organizing framework for further discussion. The annual reports of the US DEA's NFLIS (Drug Enforcement Administration's National Forensic Laboratory Information System) (USDEA 2008) provide the best insights regarding which known drugs are most used in non-medical circumstances (Table 3). The NFLIS is a system operated by the DEA that collects data generated by state and local forensic laboratories in the USA. Of all the samples analyzed in 2008 by US local and state forensic laboratories for the presence of non-medically used drugs, 25 controlled substances composed 90% of all the samples.

Of these 25 drugs, the most frequent 4 were tetrahydrocannabinol (THC), cocaine (benzoylmethylecgonine), methamphetamine, and heroin. Seven were narcotic analgesics (codeine, hydrocodone, oxycodone, methadone, morphine, buprenorphine, and hydromorphone), four were benzodiazepines (alprazolam, clonazepam, diazepam, and lorazepam), and others included 3,4-methylenedioxymethamphetamine (MDMA), 3,4-methylenedioxymphetamine (MDA), amphetamine, methylphenidate, phencyclidine (PCP), pseudoephedrine, carisoprodol, 1-benzylpiperazine (BZP), and psilocin. In addition to these top 25, other drugs frequently used for non-medical purposes included narcotic analgesics (butorphanol, dihydrocodeine, fentanyl, meperidine, nalbuphine, opium, oxymorphone, pentazocine, propoxyphene, and tramadol), benzodiazepines (chlordiazepoxide, flunitrazepam, midazolam, temazepam, and triazolam), "club" drugs [ketamine, 1-(3-trifluoromethylphenyl)piperazine (TFMPP), gamma-hydroxybutyrate/gamma-butyrolactone (GHB/GBL), 5-methoxy-*N,N*-diisopropyltryptamine (5-MeO-DIPT), and 3,4-methylenedioxymethylamphetamine (MDEA)], a number of stimulants (e.g., cathinone, ephedrine, and phentermine), and a number of anabolic steroids (e.g., methandrostenolone, nandrolone, and stanozolol). Many of these latter drugs (not the top 25) have never been routinely targeted for monitoring as environmental contaminants.

The top 25 detected by NFLIS (DEA's National Forensic Laboratory Information System) are all among the most commonly abused drugs in the USA. The major ones missing from these top 25 (but which are captured in the remaining 10% of samples analyzed by NFLIS) are barbiturates (e.g., phenobarbital and seconal, whose rate of abuse has been declining), certain benzodiazepines (such as alprazolam, chlordiazepoxide, and diazepam, but excepting flunitrazepam), methaqualone, mescaline (3,4,5-trimethoxyphenethylamine), and dextromethorphan (NIDA 2009). Extensive statistics on rates of drug use worldwide (including those maintained by

Table 3 Drugs of abuse frequently detected by US forensics laboratories^a

Among the 25 abused drugs most frequently detected by US forensics labs	Other abused drugs frequently detected by US forensics labs
<i>Most frequent</i>	<i>Narcotic analgesics</i>
Tetrahydrocannabinol (THC)	Butorphanol
Cocaine (benzoylmethylecgonine)	Dihydrocodeine
Methamphetamine	Fentanyl
Heroin (diacetylmorphine; diamorphine)	Meperidine
	Nalbuphine
<i>Narcotic analgesics</i>	Opium
Buprenorphine	Oxymorphone
Codeine	Pentazocine
Hydrocodone	Propoxyphene
Hydromorphone	Tramadol
Methadone	
Morphine	<i>Benzodiazepines</i>
Oxycodone	Chlordiazepoxide
	Flunitrazepam
<i>Benzodiazepines</i>	Midazolam
Alprazolam	Temazepam
Clonazepam	Triazolam
Diazepam	
Lorazepam	<i>“Club” drugs</i>
	1-(3-Trifluoromethylphenyl)piperazine (TFMPP)
1-Benzylpiperazine (BZP)	3,4-Methylenedioxymethamphetamine (MDMA)
3,4-Methylenedioxymethamphetamine (MDMA)	5-Methoxy- <i>N,N</i> -diisopropyltryptamine (5-MeO-DIPT)
Amphetamine	Gamma-hydroxybutyrate/gamma-butyrolactone (GHB/GBL)
Carisoprodol	Ketamine
Methylphenidate	
Phencyclidine (PCP)	<i>Stimulants</i>
Pseudoephedrine	Cathinone
Psilocin	Ephedrine
	Phentermine
	<i>Anabolic steroids</i>
	Methandrostenolone
	Nandrolone
	Stanozolol

^aUS DEA's National Forensic Laboratory Information System (USDEA 2008)

the UNODC) can be located from the web page of the Office of National Drug Control Policy (ONDCP 2009). The UNODC World Drug Report (UNODC 2009a) provides comprehensive statistics on world illicit drug supply and demand. The availability, use, and impacts of illicit drugs in the USA were most recently assessed by the National Drug Intelligence Center (NDIC 2010).

3.1 Environmental Occurrence

While drug usage patterns and prevalence vary among countries and through time, those drugs in frequent use in the USA can serve as an organizing framework for further discussion. Of the top 25 most frequently identified, non-medically used, controlled substances analyzed by US local and state forensic laboratories in 2008, only 15 have been targeted in environmental studies of illicit drugs: amphetamine, cocaine, codeine, heroin, hydrocodone, MDA, MDMA, methadone, methamphetamine, methylphenidate, morphine, oxycodone, PCP, pseudoephedrine, and THC ($\Delta 9$ -tetrahydrocannabinol). A summary of their occurrence in a variety of environmental compartments is shown in Table 4. Note that groundwater is not listed. This is because of the dearth of groundwater monitoring studies that have targeted and identified illicit drugs. One of the only such studies identified codeine in recharged groundwaters in Spain, at sub-ppb levels (Teijon et al. 2010).

Also shown in Table 4 is the occurrence information (as well as indications of negative occurrence – or data of absence) for nearly all of the other illicit drugs and metabolites that have been reported in the published literature. From these data, those analytes with absence of data (i.e., those that have yet to be targeted in monitoring studies) can be deduced. These substances with absence of data represent potential candidates for future monitoring, should they be of interest to environmental scientists, to aquatic toxicologists, or for application with FEUDS. For example, Postigo et al. (2008a) note that nor-cocacthylene and ecgonine ethyl ester have not been targeted in any monitoring study.

The occurrence data are arranged in Table 4 according to the environmental compartments for which the data apply: wastewaters, surface waters, drinking water, sewage sludge, sewage biosolids, air, banknotes, wildlife tissue, and potential for dermal transfer. Dermal transfer is a potential route of transport to immediate physical surroundings (and to sewage during bathing) for drugs excreted via sweat or applied topically (Daughton and Ruhoy 2009). Other reviews of illicit drugs in the environment are provided by Huerta-Fontela et al. (2010) and Zuccato and Castiglioni (2009). It is important to note that parent drugs or their metabolites that have never been targeted for monitoring in the environment are not listed in Table 4. Some of these substances may make likely candidates for future screening. One example is the primary metabolite of methamphetamine, *p*-hydroxymethamphetamine, which is excreted as the sulfate and glucuronide conjugates (Boles and Wells 2010).

An examination of Table 4 reveals that the drugs with the most positive occurrence data across all environmental compartments are among the top 25 detected by NFLIS – notably the following seven, codeine, morphine, methadone, amphetamine, methamphetamine, cocaine, and THC, and the primary metabolites of methadone (i.e., 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine [EDDP]), cocaine (i.e., BZE [benzoylecgonine]), and THC (i.e., 11-nor-9-carboxy-9-THC [THC-COOH]). Although widely detected in clinical and forensic drug screens, the occurrence of heroin (diacetylmorphine) in an environmental compartment is limited primarily to banknotes, because of its propensity to hydrolyze in water.

Table 4 Drugs of abuse targeted and identified in environmental compartments^a

	Wastewaters	Surface waters	Drinking water	Sewage sludge	Biosolids	Air	Banknotes	Wildlife tissue	Dermal transfer ^b
<i>Analgesics</i>									
6-AM (6-acetylmorphine; deacetylated heroin)	✓	✓	✓	✓				✓	▲
6-AC (6-acetylcodeine)		✓	✓	✓✓✓					▲
Codeine ^c	✓✓✓	✓✓✓	✓✓✓	✓✓✓					▲
Dihydrocodeine ^d	✓✓✓	✓✓✓	✓✓✓	✓✓✓					▲
Heroin (diacetylmorphine) ^c	✓✓✓	✓✓✓	✓✓✓	✓✓✓					▲
Hydrocodone ^c	✓✓✓	✓✓✓	✓✓✓	✓✓✓					▲
Morphine ^c	✓✓✓	✓✓✓	✓✓✓	✓✓✓					▲
Morphine-3 β -D-glucuronide	✓✓✓	✓✓✓	✓✓✓	✓✓✓					‡
Norcodeine	✓✓✓	✓✓✓	✓✓✓	✓✓✓					▲
Normorphine	✓✓✓	✓✓✓	✓✓✓	✓✓✓					▲
Fentanyl ^d (excreted mainly as norfentanyl)	✓✓✓	✓✓✓	✓✓✓	✓✓✓					▲
Norfentanyl	✓✓✓	✓✓✓	✓✓✓	✓✓✓					▲
Oxycodone ^c	✓✓✓	✓✓✓	✓✓✓	✓✓✓					▲
Tramadol ^d	✓✓✓	✓✓✓	✓✓✓	✓✓✓					▲
<i>Methadone</i>									
Methadone ^c	✓✓✓	✓✓✓	✓✓✓	✓✓✓					▲
EDDP (2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine)	✓✓✓	✓✓✓	✓✓✓	✓✓✓					▲
<i>Stimulants</i>									
Amphetamine ^c	✓✓✓	✓✓✓	✓✓✓	✓✓✓					▲
Ephedrine ^d /pseudoephedrine ^c	✓✓✓	✓✓✓	✓✓✓	✓✓✓					▲
Methamphetamine ^c	✓✓✓	✓✓✓	✓✓✓	✓✓✓					▲
MDA ^c	✓✓✓	✓✓✓	✓✓✓	✓✓✓					▲
MDBD	✓✓✓	✓✓✓	✓✓✓	✓✓✓					▲

Table 4 (continued)

	Wastewaters	Surface waters	Drinking water	Sewage sludge	Biosolids	Air	Banknotes	Wildlife tissue	Dermal transfer ^b
MDEA ^d	✗✓	✗	✓		✗✓				▲
MDMA ^c	✗✓	✓	✓						‡
Methylphenidate ^c									
<i>Cocainics</i>									
Benzoylecgonine (BZE)	✓✓✓	✓	✓			✓	✓		▲
Cocaethylene	✗✓✓	✓✓✓	✓✓✓						▲
Cocaine ^c	✓✓✓	✓✓✓	✓✓✓						▲
Ecgonine methyl ester (EME)	✗✓✓✓	✓	✓						▲
Norbenzoylecgonine	✓✓	✓✓							
Norcocaine	✗✓								
<i>"Club" drugs (e.g., dissociative anesthetics)</i>									
Ketamine ^d	✗✗✓	✗							
Norketamine	✗	✗							
PCP (phencyclidine) ^c	✗✓	✗	✗						
<i>Hallucinogens</i>									
LSD	✗✗✓	✗	✗✗✓						
Nor-LSD (N-desmethyl-LSD)	✗✓✓	✗	✗✗✓						
O-H-LSD (2-oxo-3-hydroxy-LSD)	✗✓✓	✗	✗✗✓						
<i>Cannabinoids</i>									
Cannabidiol (CBN)						✓✓		✓✓	
Cannabidiol (CND)						✗✓		✗✓	
OH-THC (11-hydroxy- Δ 9-tetrahydrocannabinol)	✗✓			✗✗✓					
nor-THC									
THC (Δ 9-tetrahydrocannabinol) ^c	✓✓✓					✓✓✓			
THC-COOH (11-nor-carboxy- Δ 9-tetrahydrocannabinol)	✓✓✓						✗	✗✓	

Table 4 (continued)

	Wastewaters	Surface waters	Drinking water	Sewage sludge	Biosolids	Air	Banknotes	Wildlife tissue	Dermal transfer ^b
<i>Other</i>									‡
Flunitrazepam ^d			×						
Testosterone									

“ \times ”: Frequency of negative occurrence data (data of absence); supporting data are stronger with more “ \times ” (up to two total)

✓: Frequency of positive occurrence data; supporting data are stronger with more “✓” (up to three total)

Blank cells denote lack of any type of supporting data (absence of data)

Supporting references

Wastewaters: Bartell-Hunt et al. (2009), Buijsma et al. (2009), Boleda et al. (2007, 2009), Bones et al. (2007a), Castiglioni et al. (2006, 2007), Chiaia et al. (2008), Frost and Griffiths (2008), Gheorghe et al. (2008), González-Mariño et al. (2009, 2010), Huerta-Fontela et al. (2007, 2008a, b), Hummel et al. (2006), Jones-Lepp et al. (2004), Karolak et al. (2010), Kasprzyk-Hordem et al. (2007, 2008a, b, 2009a, 2010), Khan (2002), Loganathan et al. (2009), Mari et al. (2009), Postigo et al. (2008b, 2010), Terzic et al. (2010), van Nuijs et al. (2009a), Zuccato et al. (2005, 2008a)

Surface waters: Bartell-Hunt et al. (2009), Buijsma et al. (2009), Boleda et al. (2007, 2009), Bones et al. (2007a), Gheorghe et al. (2008), González-Mariño et al. (2010), Huerta-Fontela et al. (2007, 2008a), Kasprzyk-Hordem et al. (2007, 2008a), Postigo et al. (2010), Zuccato et al. (2008b, 2005)

Drinking water: Boleda et al. (2009), Huerta-Fontela et al. (2008a)

Sewage sludge: Kafeta et al. (2006), Khan (2002)

Biosolids: Jones-Lepp and Stevens (2007)

Air: Baldacci et al. (2009), Cecinato and Baldacci (2007), Cecinato et al. (1998), Hannigan et al. (1998), Postigo et al. (2009), Viana et al. (2010)

Banknotes (small sampling of published works): Aaron and Lewis (1987), Armenta and de la Guardia (2008), Bones et al. (2007b), Carter et al. (2003), Ebeler et al. (2005, 2007), Felix et al. (2008), Jenkins (2001), Lavins et al. (2004), Sleeman et al. (2000), Zuo et al. (2008)

^aThe references providing the data for this table are listed for each of the columns. Wastewaters include both raw sewage influent and treated sewage effluent. Note that this table does not include drugs or metabolites that have never been targeted in monitoring studies, *p*-hydroxymethamphetamine is one example

^bPotential for transfer from skin to surroundings (Daughn and Ruhoy 2009): ▲ = known to be excreted via sweat; ‡ = available in high-concentration dermal transfer devices

^c15 of the top 25 most frequently identified, non-medically used, controlled substances – as analyzed and reported by US local and state forensic laboratories in 2008 (see USDEA 2008) and which comprised 90% of all drugs identified (USDEA 2008)

^dAmong the other most frequently identified, non-medically used, controlled substances – as analyzed and reported by US local and state forensic laboratories in 2008 (see USDEA 2008); the other 9 most frequently identified 25 drugs, but not yet targeted in more than a single environmental study, focused expressly on illicit drugs are alprazolam, buprenorphine, BZP (1-benzylpiperazine), carisoprodol, clonazepam, diazepam, lorazepam, and psilocin

Similarly, the cannabinoids are detected most frequently in air. Not surprisingly, no illicit drug (or metabolite) frequently reported with environmental occurrence data is missing from the 25 most frequently identified by forensic labs.

Nine of the remaining 25 drugs most frequently identified by the forensic testing labs have not yet been targeted in environmental studies whose primary focus is illicit drugs. These are alprazolam, buprenorphine, BZP (1-benzylpiperazine), carisoprodol, clonazepam, diazepam, hydromorphone, lorazepam, and psilocin (4-hydroxy-dimethyltryptamine, 4-HO-DMT). Of these nine drugs, environmental occurrence data have been published in studies targeted at CPDs for alprazolam, carisoprodol, diazepam, and lorazepam. Data do not exist for buprenorphine, BZP, clonazepam, hydromorphone, and psilocin. Depending on their pharmacokinetics and the extent to which that are excreted unchanged, these latter five drugs may be likely targets for future environmental monitoring.

Alprazolam has been measured at low to high ng/L levels in treated sewage effluent (Batt et al. 2008). Although carisoprodol is extensively metabolized (primarily to the active metabolite meprobamate), it has been measured at sub-ppb levels in runoff from agricultural fields irrigated with treated wastewater (Pedersen et al. 2005).

Diazepam has been widely reported in a variety of wastewaters and surface waters; see the summaries of Calisto and Esteves (2009) and Straub (2008). Most diazepam occurrence data from targeted monitoring, however, have been negative (Christensen et al. 2009). Diazepam resists biodegradation (Redshaw et al. 2008) and perhaps partitions to particulates.

Some illicit drug analytes, when targeted, are infrequently reported, possibly as a result of their considerably higher detection limits. Normorphine and THC-COOH are examples, sometimes having limits of detection 1–2 orders of magnitude higher than those of other analytes. This reiterates the importance of specifying limits of detection when presenting data of absence.

Other targeted analytes are not detected, probably because they are extensively metabolized or excreted as conjugates. Conjugation undoubtedly plays a critical role in determining whether a free parent drug will be found in waters. Many drug ingredients are extensively conjugated and, without a hydrolysis step to free the aglycone, will be missed (Daughton and Ruhoy 2009; Pichini et al. 2008). Conjugates could potentially serve as hidden reservoirs for drug ingredients in the environment (Daughton 2004), but, to date, published data are lacking to affirm the extent and magnitude of this phenomenon.

Lorazepam is extensively metabolized to its glucuronide conjugate, with negligible amounts excreted unchanged (Ghasemi and Niazi 2005). Nonetheless, it has been measured at levels up to 200 ng/L in treated sewage (Coetsier et al. 2009; Gros et al. 2009, 2010), perhaps reflecting an input from disposal to sewers or hydrolysis of the conjugate.

It is important to note that some illicit drugs are metabolic/transformation daughter products of others, which explains why their concentrations in sewage or receiving waters are routinely higher than those of their parents. One example is heroin, which is quickly deacetylated (both metabolically and in the environment) to 6-AM followed by hydrolysis to morphine. This means that the probability is higher that these parent drugs, when detected in waters (especially waters removed

from impact by sewage), are present because they were directly flushed into sewers (or excreted via sweat) rather than being excreted via urine. An alternative source could be runoff into streams, such as during clandestine manufacturing. Another example is fentanyl, which is extensively excreted as norfentanyl.

3.2 Adulterants and Impurities as Potential Environmental Contaminants

In contrast to pharmaceuticals produced under Good Manufacturing Practices, drugs made illegally contain significant impurities and contaminants in addition to the sought-after drug (or sometimes even in place of the desired drug). These substances are often present at very high levels, especially in intentionally mislabeled drugs – sometimes representing the bulk of the purported drug. For example, noscapine can be present at levels up to 60% in heroin, or phenacetin at levels up to 50% in cocaine. Another example is the misrepresentation of MDMA by combining 1-benzylpiperazine (BZP) and 1-(3-trifluoromethylphenyl)piperazine (TFMPP), which can mimic its psychoactive effects. These adulterants and other contaminants also include products of synthesis or processing (precursors, intermediates, by-products), natural impurities (e.g., natural product alkaloids), products of degradation (e.g., oxidation during storage), and pharmacologically active adulterants (e.g., many licit drugs and other chemicals, such as levamisole, xylazine, lidocaine, phenacetin, hydroxyzine, and diltiazem). Some of these impurities or adulterants are more potent than the sought-after drug (cocaethylene being one example – a synthesis by-product and metabolite of cocaine when consumed together with ethanol). In the course of reviewing the literature, more than 90 common adulterants and impurities were noted just for the four illicit drugs cocaine, MDMA, methamphetamine, and heroin (Table 2). These represent only a small sampling of the variety of chemicals that can compose illicit drugs.

Because some illicit drugs are natural products, they can inadvertently contaminate our food supply. The recent controversy regarding the presence of cocaine in a commercial energy drink (as residue from de-cocainized extract of coca leaf) (BfR 2009) demonstrates the power of analytical chemistry in revealing previously undetected levels of chemicals.

Adulterants are often used to enhance desired biological effects or make the drug more profitable. They include diluents, which are added to mimic the appearance of the sought-after drug (to extend the doses per mass) or enhance the biological effects. Impurities are sometimes integral to the natural chemistry of the native plant from which a drug is isolated and at other times is a function of the synthetic route to the desired drug. The adulterants used are a function of the geographic locale of manufacture/distribution or depend on what chemicals are available at the time of synthesis or what the clandestine manufacturer wishes to use. Many dozens of impurities and adulterants are possible for any given drug synthesis. Impurities, in turn, can each yield numerous metabolites, most of which are known. Adulterants can range from common substances such as caffeine (very high concentrations)

to more insidious chemicals such as the cytotoxic veterinary dewormer drug levamisole, which has led to a number of deaths from its inadvertent consumption. In this way, illicit drug use can serve as an alternative route of entry to the environment not just for drugs of abuse, but also for active pharmaceutical ingredients, such as levamisole, that have no potential for abuse. Adulteration of illicit drugs has grown to become a major health risk for drug users.

An expansive published literature exists for illicit drug adulterants and impurities. This is driven largely by research and surveillance aimed at drug “profiling,” a methodology for obtaining a chemical fingerprint or signature for individual batches of drugs. For example, determining illicit drug impurities (and ratios of enantiomers) helps deduce the synthetic route or geographic locale of manufacture. An example of the profiling process (for methamphetamine) is presented by Inoue et al. (2008). Profiling data are potentially useful for targeting important adulterants or impurities for environmental monitoring.

Except for some registered pharmaceuticals that are used as adulterants in illicit drugs (to reduce cost or alter/mimic physiologic/psychotropic effects), these adulterants pose totally unknown risks for the environment. The ecological risks for some registered pharmaceuticals used as adulterants are similarly unknown. One example is levamisole, which is excreted largely unchanged and potentially poses risks for certain soil-dwelling organisms (McKellar 1997; Sommer and Bibby 2002). It is also known to be taken up by certain food crops such as lettuce (Boxall et al. 2006a), but has not yet been targeted in any environmental monitoring. Levamisole has, however, been identified as a high-priority compound for possible future environmental monitoring (Boxall et al. 2006b).

The general public may be unknowingly exposed to illicit drugs in the form of designer drugs as impurities in food or nutritional supplements. For example, common foods may contain residues of illegal analogs of legal drugs, particularly anabolic hormones (used in livestock), such as norboletone, tetrahydrogestrinone, and desoxymethyltestosterone (Cunningham et al. 2009; Noppe et al. 2008; Shao et al. 2009; Yang et al. 2009). Certain OTC supplements used for male erectile dysfunction may contain unregistered synthetic analogs of the approved phosphodiesterase type-5 (PDE-5) inhibitors (Poon et al. 2007; Venhuis and de Kaste 2008; Venhuis et al. 2007).

4 Large-Scale Exposure or Source Assessments via Dose Reconstruction

Interest in illicit drugs in the environment has both prospective and retrospective dimensions. The prospective dimension is concerned with the exposure of aquatic organisms and humans to environmental residues. Of the environmental studies conducted, however, this has not been the major thrust. Rather, the data obtained have been used as a retrospective tool for reconstructing society-wide usage of illicit drugs. Such data acquisition could be considered a large-scale version of exposure assessment called “dose reconstruction” (e.g., see ATSDR 2009).

Dose reconstruction approaches that use the presence of drug residues on banknote currency and in airborne particulates have also been attempted. These could be more accurately referred to not as dose reconstruction, however, but rather as source reconstruction (deciphering the source and intensity of the origin of the drugs).

4.1 Sewage Epidemiology or Forensics – FEUDS

Daughton (2001c) first proposed analyzing sewage for residues of illicit drugs unique to actual consumption (rather than originating from disposal or manufacture) for the purpose of back-calculating estimates of community-wide usage rates. Since 2001, this approach has been referred to as “sewage epidemiology” (a term first reported in the literature by Zuccato et al. 2008a), “sewage forensics,” and “community-wide urinalysis” or “community drug testing.” None of these terms, however, fully captures the multiple purposes that could potentially be served by application of the methodology.

Epidemiology can be defined as the study of the occurrence, distribution, and causes of health effects in specific human populations and the use of this study as the basis for interventions targeted at reestablishing public health. Epidemiology is used for identifying at-risk subpopulations, monitoring the incidence of exposure/disease, and detecting/controlling epidemics. Elements of illicit drug use fit all of these categories. In its simplest state, “forensics” involves the extraction of pertinent information to support an argument or investigation (Daughton 2001b). One of its best known modern applications is to assist in resolving legal issues, and the worldwide legal system plays an integral role in all aspects of illicit drug use.

Since this still-evolving approach for measuring drugs in sewage to estimate collective drug usage has elements of both forensics and epidemiology, it would be more accurately captured under the newer term “Forensic Epidemiology,” which integrates the principles and methods used in public health epidemiology with those used in forensic sciences (Goodman et al. 2003; Loue 2010).

Therefore, a more accurate descriptive term for “sewer epidemiology” should be considered to better unify the published literature. One possibility could be “Forensic Epidemiology Using Drugs in Sewage” (FEUDS). Use of a unique term and acronym would have the added benefit of more easily facilitating communication across fields and to greatly simplify literature searches. The acronym FEUDS will be used as a shorthand in the remainder of the discussion here.

4.2 FEUDS for Community-Wide Dose Reconstruction of Illicit Drugs

After its conceptualization in 2001 (Daughton 2001c, d), FEUDS was first implemented in a 2005 field monitoring study by Zuccato et al. (2005). FEUDS was originally proposed as the first evidence-based approach for measuring drug use

because the long-practiced approaches that use oral or written population surveys are fraught with limitations, not the least of which involve numerous sources of potential error that are difficult to define, control, or measure (especially sampling bias and self-reporting bias) (Daughton 2001c). The limitations imposed by self-reporting bias have been corroborated in “concordance” studies (comparisons of self-report data with empirical bioanalysis data), which point to gross under-reporting by self-reports (often at rates as low as one-half of actual); the problems with profound underestimates derived from self-reporting are discussed by Magura (2010). Sampling bias inevitably results from the decision process used for selecting which segments of the general population to survey.

These conventional approaches to estimating illicit drug usage also suffer from two inherent limitations: extreme delays in time before results are compiled and reported and costs associated with data collection and interpretation.

FEUDS, like public surveys, suffers from many sources of potential error. But FEUDS is in its infancy and its sources of error derive from variables still under investigation and which have not yet been optimized for better control. While conceptually rather straightforward, the back-calculations used in FEUDS are a function of numerous variables, including demographics, population flows through a locale (such as transient visitors and commuters) served by a given sewage treatment facility, route of dose administration, pharmacokinetics (including knowledge of extent of conjugation), constancy of usage, frequency of disposal (if the parent drug rather than a unique metabolite is targeted), and sewage flows. Combined, these pose a major challenge for modeling to accurately reconstruct dose. The numerous problems facing FEUDS are discussed in Frost and Griffiths (2008) and in van Nuijs et al. (2010 – in press). Most FEUDS investigators couple drug concentrations in sewage with per-capita sewage flows to calculate what is sometimes called “index loads” or “per-capita loads,” expressed as mg/person/day. Many of the sources of uncertainty are covered by Banta-Green et al. (2009) and Zuccato et al. (2008a).

Despite the plethora of uncertainties attendant to variables involved in back-calculations, the ability to provide estimates of near-real-time community-wide usage is something that is not possible with any other known approach. This also opens the possibility of detecting real-time trends or changes in drug use. Example applications include verifying reductions in drug use as a result of interdictions or public health campaigns or detecting the emergence of newly available drugs or overall changes in drug-use patterns. Data on real-time usage could better inform decisions regarding drug control and mitigation. Correlating policy actions with resulting society-wide impacts cannot be effectively done when collected data are significantly delayed in reporting. Transient or episodic patterns are obscured when reports are on an annual basis.

Few systematic approaches to cataloging newly emerging recreational drugs (those not yet recognized in the published literature) have existed. One such attempt, conducted from 2008 through 2009, mined information collected from a broad spectrum of sources (Psychonaut Web Mapping Research Group 2010). As of March 2010, the project had categorized over 400 substances or mixtures not previously

recognized in the published literature as having recreational use. One example is mephedrone (2-methylamino-1-*p*-tolylpropan-1-one, 4-methylmethcathinone, 4-MMC, MMCAT), a substance that has experienced wide and growing popularity as a street drug in the UK but which is sold in various guises, such as “plant food” and labeled “not for human consumption.” By mid-April 2010, mephedrone had been banned in the UK, only to witness another drug enter the spotlight – 5,6-methylenedioxy-2-aminoindane (MDAI) – developed in the 1990s as an antidepressant. This exemplifies the speed at which a continual series of new chemicals is embraced by recreational drug users.

It is of great potential significance that there are no apparent technical obstacles to designing automated continuous monitors for use in sewage collection/distribution systems. Implementing continuous monitoring to support FEUDS could greatly enhance efforts to control and mitigate drug use. Such a hypothetical system could use a number of different approaches, generally based on the use of in-stream chemical sensors or automatic acquisition of discrete samples at pre-selected intervals followed by instrumented auto-analysis. The limiting factor would be cost. The foundation for continuous monitoring is already being established, especially for use in clinical and forensics laboratories. One such automated method has been applied to 21 commonly abused drugs in urine, using online extraction coupled with tandem mass spectrometry (Chiuminatto et al. 2010); the main area of needed improvement is sufficiently low limits of detection.

Another advantage of FEUDS over population surveys is that not all drug use is necessarily known to the users themselves, who then unintentionally report incorrect drug identities and usage quantities. Illicit drug users often do not know the identity or the quantity of the active substances they have consumed because the purity of what they consume is unknown. Often, the active substance or quantity is not what the distributor claims (e.g., counterfeit illicit drugs). Adulterants are often substituted (Table 2), in part or in whole, for the purported drug. One general route of such uninformed exposure is the surreptitious incorporation of designer drugs into otherwise legal OTC diet supplements or recreational or lifestyle products. An example is the relatively new (and probably still incompletely characterized) synthetic analogs of the approved phosphodiesterase type-5 (PDE-5) inhibitors (used primarily in treating erectile dysfunction), such as sildenafil, vardenafil, and tadalafil (Poon et al. 2007; Venhuis and de Kaste 2008; Venhuis et al. 2007). In more than half of the OTC male erectile dysfunction health products examined, analyses revealed the presence of acetildenafil, hydroxyacetildenafil, hydroxyhomosildenafil, and piperidenafil – analogs of sildenafil and vardenafil not registered for pharmacologic use. The legal registered versions of PDE-5 inhibitors have only recently been detected in wastewaters (Nieto et al. 2010). Since members of this class of drugs all share the same mechanism of biological action, the PDE-5 inhibitor analogs could contribute to dose additivity. Analogs are known to exist for various other classes of drugs, particularly psychoactives, anabolic steroids, and anti-obesity drugs. The toxicity of these analogs is largely unknown. The extent of such adulteration in the drug and supplements industry is unknown, largely because the targets for analysis are often not known to forensic analysts.

Hagerman (2008) provides a brief history of FEUDS projects in the USA. The ONDCP performed the first FEUDS monitoring in the USA in 2006, targeting about 100 wastewater treatment plants (WWTPs) across two dozen regions (Bohannon 2007). The first conference devoted to FEUDS was organized by EMCDDA in Lisbon, Portugal, in April 2007 (EMCDDA 2007). It led to the first published overview of many of the aspects of the topic (including scientific, technical, social, privacy, ethical, and legal concerns), as provided by Frost and Griffiths (2008).

4.3 Quality Assurance and FEUDS

Two aspects of illicit drugs may have a major impact on the quality and validity of any monitoring data used for FEUDS. The first is the contamination of samples during collection or analysis by transfer of residues from the skin of the analyst. Many drugs, especially illicit drugs, are readily excreted via sweat glands, including those on the fingers. This has the potential to result in contamination of samples during their collection or during various steps in analysis. Contamination of samples by analysts who are using prescribed or illicit drugs is an under-investigated potential source of erroneous data. The dermal excretion of drugs as a source of their transfer to immediate surroundings as well as to the environment was first examined by Daughton and Ruhoy (2009).

The second aspect is the stability of drug residues in samples in the absence of proper preservation. Little research has been done on the stability of illicit drugs in collected environmental samples; the extensive existing literature on the stability of residues in biological samples obtained for forensics and human drug monitoring purposes may be partly relevant and could serve as a starting point for environmental samples. Both cocaine and cocaethylene, for example, have been shown to readily degrade to benzoylecgonine (Castiglioni et al. 2006). González-Mariño et al. (2010) examined the preservation of raw sewage samples with sodium azide at 4°C to inhibit microbial degradation of labile analytes such as cocaine and cocaethylene. In time-course studies up to 7 days, large positive or negative changes in concentrations were noted for methadone, cocaine, benzoylecgonine, heroin, morphine, and THC-COOH. They concluded that sample preparation (e.g., solid phase extraction followed by any needed derivatization and storage at low temperature) was best performed as soon as possible at the site of sample collection.

4.4 Summary of Published Research in FEUDS

Overviews and discussion of the FEUDS studies published up until 2008 are provided by Postigo et al. (2008a), van Nuijs et al. (2010 – in press), and Zuccato et al. (2008a). The major published articles regarding one or more aspects of the FEUDS approach are compiled in the chronology of Table 5. At the beginning of 2010, there had been fewer than two dozen studies, and most were published after 2007.

Table 5 Major FEUDS studies (arranged according to chronology)

Year	Title (citation)
2001	Illicit drugs in municipal sewage: proposed new non-intrusive tool to heighten public awareness of societal use of illicit/abused drugs and their potential for ecological consequence (Daughton 2001c) Commentary on illicit drugs in the environment: a tool for public education – societal drug abuse and its aiding of terrorism (Daughton 2001d)
2005	Cocaine in surface waters: new evidence-based tool to monitor community drug abuse (Zuccato et al. 2005)
2006	High cocaine use in Europe and US proven Stunning data for European Countries: first ever comparative multi-country study of cocaine use by a new measurement technique (Sörgel 2006)
2007	Using environmental analytical data to estimate levels of community consumption of illicit drugs and abused pharmaceuticals (Bones et al. 2007a)
2008	Occurrence of psychoactive stimulatory drugs in wastewaters in north-eastern Spain (Huerta-Fontela et al. 2008b) Estimating community drug abuse by wastewater analysis (Zuccato et al. 2008a) Assessing illicit drugs in wastewater: potential and limitations of a new monitoring approach (Frost and Griffiths 2008)
2009	Cocaine and metabolites in waste and surface water across Belgium (van Nuijs et al. 2009b) Cocaine and heroin in wastewater plants: a 1-year study in the city of Florence, Italy (Mari et al. 2009) Monitoring of opiates, cannabinoids, and their metabolites in wastewater, surface water, and finished water in Catalonia, Spain (Boleda et al. 2009) Can cocaine use be evaluated through analysis of wastewater? A nationwide approach conducted in Belgium (van Nuijs et al. 2009c) Illicit drugs and pharmaceuticals in the environment – forensic applications of environmental data, Part 1: estimation of the usage of drugs in local communities (Kasprzyk-Hordern et al. 2009b) Municipal sewage as a source of current information on psychoactive substances used in urban communities (Wiergowski et al. 2009) The spatial epidemiology of cocaine, methamphetamine, and 3,4-methylenedioxymethamphetamine (MDMA) use: a demonstration using a population measure of community drug load derived from municipal wastewater (Banta-Green et al. 2009)
2010	Drugs of abuse and their metabolites in the Ebro River basin: occurrence in sewage and surface water, sewage treatment plants removal efficiency and collective drug usage estimation (Postigo et al. 2010) Estimation of illicit drugs consumption by wastewater analysis in Paris area (France) (Karolak et al. 2010) Illicit drugs in wastewater of the city of Zagreb (Croatia) – estimation of drug abuse in a transition country (Terzic et al. 2010) Illicit drug consumption estimations derived from wastewater analysis: a critical review (van Nuijs et al. 2010 – in press)

Published FEUDS analyses have been conducted in a number of countries, with assessments at local, regional, or national levels – primarily in Belgium, Germany, Ireland, Italy, Spain, Switzerland, the USA (i.e., Oregon), and Wales. To date, FEUDS assessments have been focused on a select few parent drugs

(primarily cannabis, cocaine, heroin, and MDMA) using various metabolites. They have been performed using many sampling methodologies – ranging from 1-day single-event discrete grab sampling to longer term (e.g., 12-month) integrative continuous sampling over numerous WWTPs or rivers, servicing regions with populations exceeding millions. In many of these studies, temporal usage patterns were investigated, in which yearly seasons or the day of the week (e.g., higher cocaine use on weekends) was examined. Usage rates are reported on various comparative bases, often involving per capita (e.g., g/day/1,000 population – usually ranging only up to several grams), total consumption (e.g., tonne per year per geographic area), or flows (mass/river/day). Discrete monitoring must acknowledge the cyclic or episodic drug-use pattern fluctuations in concentrations that can result from diurnal cycles, seasons, or day of the week. This can be particularly pronounced for recreational drugs.

An enormous published literature surrounds the forensic chemistry of illicit drugs. The numbers of illicit drugs analyzed in the environment, however, is a small fraction of those that have been targeted in countless studies published on biological tissues and fluids for the purposes of forensics and patient compliance monitoring and for the study of pharmacokinetics in animals. Accurate-mass (exact-mass) identification of unknowns (e.g., via time-of-flight mass spectrometry – TOF-MS) plays a central role especially when authentic reference standards are not available. While this conventional forensics literature can serve as a guide for environmental analysis, it is only indirectly relevant. There are numerous variables involved with (and impacting) the procedural steps used in the analyses required by FEUDS – ranging from sampling design and matrix interferences to analyte determination and the need for extremely low limits of detection. Some major overviews and discussion of the analytical approaches for measuring illicit drugs in wastewaters and other waters are available (Castiglioni et al. 2008; Postigo et al. 2008a; Zuccato and Castiglioni 2009).

With interest in trace environmental contaminants (or micro-constituents) continuing to grow, a critical and limiting factor in gaining a comprehensive and accurate picture is the limit of detection (LOD) – and allied figures of merit such as the limit of quantitation (LOQ). LOD and LOQ are functions of the individual analyte as well as the matrix in which it occurs; raw sewage, for example, is a particularly problematic matrix, giving significantly higher LODs than drinking water. As a key figure of merit, the LOD dictates the extent to which environmental monitoring produces meaningful data of absence (negative occurrence data); it is roughly defined as the lowest concentration that an analytical method can differentiate with statistical power from background signal. With discussions of the formal definition of the LOD aside, one ramification is that LODs can differ widely among analytes (and among methods). Therefore, data of absence cannot be directly inter-compared without providing the context of their respective magnitudes. The absence of two drugs in a sample, for example, has different meanings when their LODs differ by 1, 2, or even more orders of magnitude. To state that a drug is not found in a certain sample is rather meaningless without specifying its LOD. For most of the

monitoring studies cited in this chapter, LODs were provided as part of the method development. For illicit drugs in sewage, LODs tend to settle in the 1–10 ng/L range, with excursions to either side. Some drugs have higher LODs – possibly a reason for sporadic occurrence data. One example is 6-acetylmorphine, whose LOD can be an order of magnitude higher than for others, such as cocaine and cocaethylene (Postigo et al. 2008b).

An issue little addressed in FEUDS studies has been the complications (and opportunities) posed by chirality. Only recently has attention begun to be directed to the speciation of enantiomers during environmental analysis (Kasprzyk-Hordern et al. 2010). Possibly the majority of illicit drugs have at least one chiral center (Smith 2009). The alkaloid truxilline, as an example, occurs in coca leaf as 11 stereoisomers. Amphetamines can each have a pair of enantiomers, sometimes distinguishing the licit from the illicit form (as well as portending relative toxicity). This may account for a portion of some of the large variance in estimated amphetamine usage across FEUDS studies. While chiral isomers can pose difficult challenges for analytical chemists, they also provide a wealth of forensics information in terms of chemical “fingerprinting” – for example, in distinguishing legal from illegal origins. Advancements in the application of chiral analysis to illicit drugs in the environment will most likely accelerate, especially in its use for FEUDS.

4.5 Legal Concerns Surrounding FEUDS

Application of FEUDS to analysis of co-mingled sewage (such as at a sewage treatment facility) clearly ensures the anonymity of individuals, which was one of its primary features when first proposed (Daughton 2001c, d). Even though FEUDS was conceptualized for public health purposes, the potential for its abuse in law enforcement was recognized early. An obvious scenario where privacy could be breached would be the implementation of sewage monitoring as close to individual sewer feeder lines as possible to trace the origin of illicit drug residues back to specific, individual neighborhoods or isolated buildings. Despite this tacit understanding as far back as 2001, there has been little formal discussion of legal or ethical issues in the published literature, even in law journals; interest in more specific, localized application of FEUDS is evident from statements such as whether it “can be used in smaller communities in which illicit drug use is especially unwanted such as drug rehabilitation centers, hospitals, prisons, military compounds and schools” (Verster 2010). One of the only, and certainly the most comprehensive, examinations of the legal concerns (in the USA) was published by Hering (2009). The concerns center primarily on the Fourth Amendment (unreasonable searches) and the potential for violating an individual’s privacy. Although the historical summary of events behind FEUDS is not fully accurate, Hering presents a comprehensive examination of the pitfalls involving US law, using case law to substantiate the concerns. He concludes, however, that although FEUDS applied to the sewers of an isolated

home might appear to constitute a search under the Fourth Amendment, the legal case would be “extremely tenuous.”

5 Illicit Drugs in the Money Supply

Residues of illicit drugs have been known since the 1980s to occur on banknotes (e.g., Aaron and Lewis 1987; Table 1), primarily as a result of dermal transfer from drug users and transfer from contact with bulk drugs themselves. Highly contaminated banknotes can, in turn, cross-contaminate pristine banknotes in their proximity. Most research has been focused on cocaine, because of its propensity to become entrapped in banknote fibers and because of the use of banknotes for insufflation. Cocaine amounts exceeding 1 mg per banknote have been reported (Oyler et al. 1996), more than 1% of a typical dose. The contamination may be so pervasive that large numbers of banknotes must be removed from general circulation each year (Thompson 2002). Bones et al. (2007b) pushed the limit of detection for cocaine into the range of a picogram per banknote. In addition to cocaine, other drugs studied on banknotes include 6-AM, diacetylmorphine (DAM), $\Delta 9$ -tetrahydrocannabinol, cannabinol, cannabidiol, 3,4-methylenedioxymethamphetamine, methamphetamine, amphetamine, PCP, and codeine.

Although the occurrence of illicit drugs on money in general circulation possibly serves as a minor source of exposure for the public, via dermal transfer and pulmonary exposure (but especially among those working with money sorting machines), no exposure work has been done on these routes. Interest has been spurred instead by forensics – primarily with the potential to distinguish “drug money” from “innocent” money. Because of the widely varying drug-use practices and patterns across countries and cultures, very different patterns of money contamination by drugs occur. Correlations of contamination with the source of money, however, have been weak. The degree of contamination is partly a function of the denomination of the banknote; in the USA, for example, denominations \$5 through \$50 have contained higher cocaine residue levels than \$1 and \$100 denominations. While banknote contamination can give an indication of types of drugs in use and especially recent proximity to bulk drug supplies, it has not provided insights on societal usage rates.

The forensics aspects of drug-contaminated money have been advanced largely by the work of investigators with Mass Spec Analytical Ltd. (MSA 2007). Overviews are available from Sleeman et al. (2000) and Armenta and de la Guardia (2008). Numerous papers have been published, a few of which are Bones et al. (2007b), Burton (1995), Carter et al. (2003), Ebejer et al. (2005, 2007), Jenkins (2001), Lavins et al. (2004), Luzardo et al. (2010), Sleeman et al. (1999), and Zuo et al. (2008).

This field will surely benefit from the rapid screening capabilities of ambient ionization mass spectrometry (e.g., Chen et al. 2009). Clearly, the potential exists for transfer of minute residues of illicit drugs from circulating money to the public; the ramifications of this, if any, are unknown.

6 Illicit Drugs in Ambient Air

Unlike the vast majority of pharmaceuticals, certain illicit drugs have the potential to escape to the ambient air, primarily because of the release of vapors and particulates from smoking and inhalation and from the generation of dusts; some of the only pharmaceuticals studied in air are the genotoxic chemotherapeutics used in the occupational setting (see references cited in Daughton and Ruhoy 2009). Perhaps the first data on an illicit drug in the environment were the 1998 report of cocaine associated with particulates in Los Angeles ambient outdoor air (Hannigan et al. 1998). Since then, studies have actively targeted a limited array of illicit drugs in ambient air in several locales, primarily cities in Italy and Spain, but also in Serbia, Portugal, Algeria, Chile, and Brazil.

An overview of this topic is provided by Postigo et al. (2010). The major studies include Balducci et al. (2009), Cecinato and Balducci (2007), Cecinato et al. (2009a, b, 2010), and Viana et al. (2010); another base of knowledge regarding analytical methodologies exists in the forensics literature, such as the work of Lai et al. (2008). Residues are usually associated with airborne particulates. Concentrations of cocaine generally are in the low picograms per cubic meter but can range up to low nanograms per cubic meter. Levels within a geographic region can vary by 2 or more orders of magnitude and are sensitive to weather conditions and time of year (with higher concentrations in winter) (Cecinato et al. 2010). These highest levels are roughly 3 orders of magnitude lower than commonly found for caffeine or nicotine. Also targeted in air studies have been other cocaine-related chemicals such as BZE and cocaethylene, as well as amphetamines, cannabinoids, cocaineics, heroin, lysergics, methadone, and opioids. Multi-analyte air analysis has been rare, the work of Viana et al. (2010) being a recent example, with eight analytes targeted; this is one of the only reports of 6-AM in air.

The objective of air monitoring for illicit drugs is more in line with forensics (as a tool in detecting trends in drug usage) than with concerns regarding public health impacts from chronic pulmonary exposure to trace ambient levels. This is because cumulative lifetime doses (for example, with cocaine), even in locales with higher contamination, are 2–3 orders of magnitude below that of a single recreational dose (Cecinato et al. 2010; Viana et al. 2010). Atmospheric levels of illicit drugs, however, may be more transient and variable than levels in wastewater, adding greater complexity to its use as a tracking tool for drug usage.

7 Other Routes of Illicit Drug Impact on the Environment

7.1 *Clan Labs*

Clandestine drug laboratories (clan labs) are a primary localized source of certain drugs to the environment. Acute and chronic human health risks have been documented via all major exposure routes: inhalation, dermal absorption, and ingestion. Clan labs have been a recognized environmental hazard since the late 1980s

(Gardner 1989). Direct and collateral environmental impacts even from ephemeral production sites and facilities can be extensive (Cohen et al. 2007). Damage can result from negligent dumping of hazardous reagents and solvents, uncontrolled discharge of product chemicals and intermediates, alteration to watersheds (e.g., facilitation of erosion), and indiscriminate application of pesticides and fertilizers. In the USA, these impacts result primarily from production of cannabis and methamphetamine. Concerns are related not just to the synthesized parent drug (primarily methamphetamine in the USA) but also to the numerous synthesis starting materials and by-products (Snell 2001). With methamphetamine clan labs, a particularly problematic aspect is the insidious contamination of building structures (National Jewish Medical and Research Center 2005), in which large amounts of product permeate porous materials, creating reservoirs that serve as a perpetual source for future exposure. Morbidity from occupational and incidental human exposures is not trivial (Thrasher et al. 2009). The US EPA has issued new guidance for the cleanup of clan labs (USEPA 2009a).

Of particular interest is the financial liability and health risk posed by the purchase of contaminated real estate by unwary buyers (e.g., see Jarosz 2009; Poovey 2009). Methamphetamine-contaminated real estate has grown sufficiently common that it has fostered commercial enterprises specializing in the detection of methamphetamine (and other illicit drug) residues in real estate.

Worth noting is that wastewaters from pharmaceutical manufacturing facilities, which include both production and formulation facilities, had been largely ignored as a potential source of drug ingredients until the mid-2000s. The first survey of wastewaters from several manufacturing facilities in the USA revealed the presence of several drugs of abuse at levels over 1,000 µg/L (Phillips et al. 2010). Historically, reported levels of APIs have generally been 3 or more orders of magnitude lower than this in wastewater streams from municipalities not receiving manufacturing waste. This raises the possibility that in some locales pharmaceutical manufacturing could be a major source of certain drugs of abuse in ambient waters.

7.2 *Livestock and Racing Animals*

A wide spectrum of pharmaceuticals are known or suspected of being used illegally in livestock, primarily as growth promoters. An extensive literature exists on this subject, but due to the clandestine nature of the practice, an accurate picture does not exist for its full scope and magnitude, which probably varies greatly among countries. Some of these drugs are also abused by humans, so they can serve as another source contributing to environmental residue levels; others are unique to veterinary practice. Among the drugs in use, many may be registered for veterinary use but not for the purposes actually employed. Others may not be approved for any purpose. Included are members from the following classes: anthelmintics (e.g., levamisole), a wide range of antibiotics, coccidiostats (e.g., nitrofurans), hormones (anabolic steroids, corticosteroids, and thyreostats such as the thiouracils), β -agonists (e.g.,

clenbuterol), and tranquilizers (e.g., ketamine, haloperidol, xylazine) (Courtheyn et al. 2002; Stolker and Brinkman 2005).

Pharmaceuticals are known to contaminate much of the surroundings with which racehorses come into contact (or which their urine or sweat contacts), including stalls and racetracks (Barker 2008). Although the drugs detected in this monitoring study were primarily conventional non-steroidal anti-inflammatories (phenylbutazone, flunixin, and naproxen), analogous routes of contamination would not be unexpected for any illicit drug that may be surreptitiously used.

7.3 Dermal Contact and Transfer

Dermal transfer as a route of exposure for drugs has been an under-recognized aspect of drugs and the environment. The first comprehensive review of the ramifications of transfer of drugs from humans to the surfaces of any items contacted in the immediate surroundings (and to other people) by way of dermal transfer is provided by Daughton and Ruhoy (2009). There are two contributing factors. One is the transfer of residues remaining from topically applied drugs (which are generally applied at very high levels). The second is the excretion of systemic residues in sweat. Both factors apply equally to drugs of abuse and illicit drugs, especially potent analgesics such as fentanyl. The overall significance of this route of transfer to the immediate environment is not yet known.

7.4 Diversion

Diversion of licit drugs is the major route by which licit pharmaceuticals enter illicit markets and illicit use. Major routes include purchase from Internet pharmacies and theft from manufacturers, distributors, brick and mortar pharmacies, health-care facilities, and homes (e.g., for teen “pharming”). Pharmaceuticals still in clinical trials and not yet approved are even subject to diversion. A recent example is the selective androgen receptor modulator Andarine (a trifluoromethyl-arylpropionamide), which was being sold via the Internet to bodybuilders (Thevis et al. 2009).

Doctor/hospital shopping is also a form of diversion. A recent study of Internet pharmacies found that of nearly 3,000 online pharmacies (nearly half hosted in the USA), with combined annual sales of nearly US \$12 billion, only 2 were certified by the Verified Internet Pharmacy Practice Sites (VIPIPS) program, which is run by the National Association of Boards of Pharmacy (Felman 2009), and 10% stated that no prescription was required. Evidence points to diversion (as well as counterfeiting) as major sources for many of these drug stocks. The so-called rogue Internet pharmacies are documented as a significant source for diverted CPDs, especially Schedule III and Schedule IV drugs (NDIC 2009). Importation of drugs outside the regulatory system of the USA is a source of drugs with unknown magnitude. Estimates from the US Food and Drug Administration (FDA) have ranged from millions to

tens of millions of packages of prescription drugs per year. These include counterfeit drugs, which include a wide array of undeclared active ingredients as well as undocumented designer drugs. Importation is a complex issue. An overview is provided by the US Government Accountability Office (USGAO 2005).

In addition to widespread outlets for illegally purchasing drugs of abuse, abusers have created a wide array of methods for “legally” diverting drugs. These include not just “doctor shopping” but also “hospital shopping.” The latter is a practice in the USA that involves using free emergency services to acquire drugs to support addiction (Sullivan 2009).

7.5 Disposal of Leftover Medications

One particular aspect of drug occurrence in the environment can add significant confusion to assessing whether the source is from illicit or legal usage. For those drugs that share both legal and illicit usage (namely, those controlled substances not listed on DEA’s Schedule I), a potentially major route by which their active ingredients can directly enter the environment is by flushing into sewers. While prudent practice for disposal of leftover drugs has generally shifted away from flushing (a practice long favored in order to reduce the incidence of intentional and unintended poisonings in the home), current guidance in the USA still recommends flushing a select list of drugs. As of June 2010, this list comprised 27 drugs, all of which are commonly abused or that pose inordinate risks of poisoning and therefore are hazardous if disposed into trash; they primarily contain the active ingredients fentanyl, hydromorphone, meperidine, methadone, morphine, and oxycodone (USFDA 2009). Some of these drugs (especially fentanyl) are formulated in delivery devices such as transdermal patches. After these devices have been expended, a significant portion of the active ingredient remains. These devices often contain large amounts of active ingredient. A used drug device can contribute quantities of the active ingredient that would exceed the amount that would otherwise be excreted after oral dosage. This is explained in Daughton and Ruhoy (2009).

8 Illicit Drugs and Environmental Impact

With the exception of the immediate and overt and hidden environmental impacts from clan labs, little is known about the potential actions of illicit drugs in the environment.

8.1 Fate and Transport

Compared with pharmaceuticals, little attention has been devoted to the environmental fate and transport of illicit drugs. Most illicit drugs have never been

monitored in biosolids or sediments. Domènech et al. (2009) used fugacity modeling to predict the fate of cocaine and BZE. The microbial degradation of methamphetamine has been reported by Janusz et al. (2003). Wick et al. (2009) examined biological removal in activated sludge and found rapid removal for morphine, codeine, dihydrocodeine, oxycodone, and methadone but not for tramadol.

In two studies, the sorption of illicit drugs to sediments was reported (Stein et al. 2008; Wick et al. 2009). Wick et al. (2009) and Barron et al. (2009) acquired low distribution coefficients (K_d) for amphetamine, cocaine, cocaethylene, BZE, MDMA, morphine, codeine, dihydrocodeine, methadone, and tramadol, showing that removal via sorption to sewage sludge is possibly negligible.

8.2 Ecotoxicology

Far more is known regarding the ecotoxicology of licit pharmaceuticals than of illicit drugs, especially with regard to low-level mixed-stressor exposures. Almost nothing is known regarding the potential for biological effects in aquatic systems or the bioconcentration in biota of illicit drugs. Aquatic exposures are the primary focus.

To date, bioconcentration data for drugs of abuse have been reported in two studies. Diazepam is one of the only drugs with substantial illicit usage whose presence has been targeted in aquatic tissues. Diazepam was detected in all 10 fish liver samples analyzed from turbot at wet-weight concentrations ranging from 23 to 110 ng/g (Kwon et al. 2009). Diazepam is commonly detected in wastewaters from slaughterhouses (in China), albeit at low levels up to 16 ng/L (Shao et al. 2009), which shows that its illicit use extends beyond humans. Tramadol has been reported in the plasma of fish (up to 1.9 ng/g) exposed to treated sewage effluent (Fick et al. 2010).

The potential for effects from low-level exposure of fish is further complicated by the complexities in extrapolating across species. Data from the first in-depth study of an ectotherm with any analgesic (i.e., morphine) comport with extreme variability between species (Newby et al. 2006).

Gagne et al. (2006) report some nominal effects data from morphine in mussels. Scott et al. (2003) reported on the absence of adverse effects on soil microbial enzyme activity by six substances used in amphetamine synthesis, including P2P (phenyl-2-propanone), ephedrine, methamphetamine, and 3,4-methylenedioxymethamphetamine.

Pharmacological studies of biological endpoints at ultra-low doses have relevance to the potential for both human and ecological effects from exposure to ambient residues in the environment, especially drinking water. Some of the pioneering studies relevant to ultra-low doses were conducted in the early 1990s and showed that biological effects could be obtained at doses many orders of magnitude lower than therapeutic doses; one example is the work of Crain and Shen (1995), who reported on the nociception in mice treated with doses as low as the femtomolar range. The subject of ultra-low dose effects has been discussed with respect to exposure to pharmaceuticals in drinking water (Daughton 2010 – in press).

9 The Future

Future work to address the various environmental aspects of illicit drugs in the environment would benefit from a comprehensive assessment of what has been accomplished to date and what new research is needed. Although the knowledge base regarding all aspects of illicit drugs in the environment is extremely small compared with that of pharmaceuticals, the body of published data is perhaps sufficiently large that we risk duplication of efforts while failing to address the more important remaining gaps or needs (Daughton 2009a). The first step in ensuring better-targeted research could be the creation of a centralized, publicly accessible database of results from research conducted worldwide. Such data should include both environmental occurrence data and data of absence (covering compartments such as sewage influent and effluent, sludge/biosolids, surface water, groundwater, and drinking water, air, wildlife tissues, and money), ecotoxicology (both field and controlled exposures), and especially data generated from FEUDS studies; metadata such as GIS (geographic information system), sampling and analytical methodologies, quality assurance, detection limits, and measures of range or variance are essential.

9.1 Advancing the Utility of FEUDS

Advancement of FEUDS as a topic of research as well as a population-level survey tool could occur on two fronts. First, numerous improvements could be made to better define and control the many variables contributing to uncertainty in FEUDS back-calculations for gauging collective drug usage. Standardized methodologies are needed, with better understood and controlled sources of error. The methodologies currently used for analysis of environmental samples for illicit drug ingredients span a wide range; this can be readily seen just for amphetamine and methamphetamine (e.g., see Boles and Wells 2010). Standardized methods are especially important for facilitating more meaningful inter-comparison of FEUDS data. Data from FEUDS studies also need to be assessed more rigorously against more comprehensive user surveys to better understand the accuracy and value of both approaches.

For FEUDS to succeed as a tool in gauging illicit drug usage for epidemiologic or forensic purposes, one variable in particular needs to be better understood – the pharmacokinetics (PK) of each drug, especially as it pertains to the excretion of unchanged parent drug and metabolites (especially conjugates); the importance of thoroughly understanding PK and conjugate excretion has been addressed by Daughton and Ruhoy (2009). PK parameters are key to accurate dose reconstruction. Although excretion rates for many pharmaceuticals are not well defined, even less is known about the PK of illicit drugs. PK and its poorly defined variability within a population contribute great uncertainty to the back-calculations used with FEUDS. Many factors contribute to the broad range of expression in population PK; genetic

variability (such as single nucleotide polymorphisms) may lead to inter-occasion variability for the individual – partly as a function of environmental influences and physiological rhythms. The role of pharmacokinetics and environmental influence on drug metabolism is discussed in Daughton and Ruhoy (2009, 2010).

A comprehensive sensitivity analysis (which has yet to be performed) could possibly reveal that small changes in variables such as excretion rates (especially for extensively metabolized drugs) can lead to large errors in FEUDS calculations. For those drugs/metabolites with highly variable excretion rates, the error range could be substantial. As a case in point, with a study of 12 methamphetamine addicts, the urine ratio of amphetamine/methamphetamine ranged over 2 orders of magnitude – from 0.03 to 0.56 (Kim et al. 2008). This would also prove problematic for allocating amphetamine loadings in sewage to methamphetamine use versus medical use. A host of factors contribute to PK variability, including route and size of dose, gender, age, body mass, kidney and liver function, chronobiology, diet, polypharmacy interactions, and genetics/epigenetics (namely pharmacogenomics, which dictates the spectrum of PK variability). Similarly, it is important to be able to distinguish bacterial transformations in sewage (and the ambient environment) from those of human metabolism (Boleda et al. 2009).

Other potential ways to reduce errors in FEUDS calculations could be viewed as analogous to using internal correction methods such as internal standardization and isotope dilution. For example, instead of using correction factors based on modeling assumptions for dilution by waste streams and sewage transformations, correction factors could possibly be empirically derived by monitoring for particular pharmaceuticals. Pharmaceuticals that would be most useful for “calibrating” a WWTP system would be those that (i) are widely prescribed, (ii) are not abused or used recreationally, (iii) have real-time prescription sales data, (iv) are known to have high patient compliance (minimal leftovers, resulting in little disposal into sewers) and are used in short-term courses (not maintenance medications), (v) have a profile similar to that of the target illicit drug with regard to biodegradation and sorption to sewage solids, and (vi) have well-understood pharmacokinetics (preferably poorly metabolized, resulting in extensive excretion unchanged). By comparing the known consumption rates of the pharmaceutical “calibrant” (from prescribing databases) with the levels actually detected in the sewage stream, more accurate correction factors could possibly be derived and then applied to the illicit drug. By gathering long-term time-course data for the calibrant pharmaceutical, additional uncertainty could possibly be removed from the calibration factor. An example of a substance that may prove useful as a calibrant could be a metabolically refractory pharmaceutical such as iopromide – a widely used x-ray contrast agent with ubiquitous presence in sewage and natural waters. This approach, however, cannot remove the confounding of dual inputs from excretion and disposal of the targeted illicit drug; the latter, however, probably leads to episodic spikes in underlying baseline levels, which would become clearer with sustained monitoring.

The second front for improving the utility of FEUDS would be to expand its scope to tackle questions other than simply monitoring or gauging illicit drug

consumption. Unexplored possibilities range from early detection of emerging trends in abuse of mainstream pharmaceuticals and in their illegal trafficking (e.g., from diversion or Internet purchases) to better gauging medication compliance rates for patients. For example, with access to real-time, local prescription data, those pharmaceutical ingredients in sewage whose back-calculated usage rates are substantially higher than the prescribed rates could be targeted for investigating the possibility of illegal trafficking. A possible example can be seen in the data presented by Kasprzyk-Hordern et al. (2009b; see Table 7 therein), in which calculated usage rates for more than two dozen prescribed and OTC pharmaceuticals are compared with known nationwide (not local) dispensing rates. Of these drugs, the calculated average usage rates exceeded the national average sales by over an order of magnitude for only one drug – tramadol. Indeed, tramadol (an opioid) is recognized for its growing incidence of misuse and abuse. Real-time prescription data are greatly confounded, however, by the inability of current tracking systems to correlate location of dispensing with place of actual use (e.g., because of transient populations and mail-order prescribing) (Ekedahl and Lindberg 2005). Another expanding source of data that could potentially be used to ground truth calculated usage rates is the growing network of collection programs that take back leftover consumer medications (see Glassmeyer et al. 2009).

An important aspect of FEUDS is that it has set the foundation for the use of sewage monitoring for other purposes – some unrelated to drug use. A fascinating possibility would be the use of sewage monitoring for measuring indicators of community-wide health status via the presence of various biomarkers of health or disease (discussed below).

9.2 Real-Time Monitoring of Community-Wide Health and Disease: Using Sewage Information Mining (SIM)

Within sewage is hidden a wealth of highly complex but chaotic chemical information about myriad aspects of biological processes. In the last 5 years, we have witnessed probably only the beginning of the applications for which sewage data could prove useful, namely FEUDS. Possibly first noted in 2008, Zuccato et al. (2008a) briefly mentioned that monitoring sewage “has the potential to extract useful epidemiologic data from qualitative and quantitative profiling of biological indicators entering the sewage system.”

Perhaps the most important information contained in sewage resides with the countless biomarkers – substances that could serve as collective measures of community-wide health or disease. Biomarkers could serve as composite measures of exposure, stress, vulnerability to disease or overt disease, or health. Biomarkers include endogenous biochemicals produced in response to stress or indicative of health; they also include adducts of endogenous chemicals and xenobiotics. And of course, they include metabolites of significant detoxication or intoxication

processes from xenobiotic exposure. Suitable markers could not have pharmaceutical equivalents, which would add great complexity to the modeling process because of the need to distinguish natural from anthropogenic sources; an example of an endogenous biomarker that has exogenous pharmacological use is cortisol (hydrocortisone).

As community-wide measures of health or disease status, a new discipline of SIM could provide, for the first time, the ability to gauge collective population-wide health and disease in real time. SIM would constitute the first true application of sewage chemistry to epidemiology and provide a means for conducting epidemiology in near-real time. SIM could also create the opportunity to view communities from a new perspective – “communities as the patient” – perhaps eventually leading to the paradigm of combining human and ecological communities as a single patient – as an interconnected whole. SIM could greatly expand our limited abilities for examining associations between human health and a host of environmental variables and stressors. It could hold the potential for greatly reducing the time and expense involved with establishing linkages between human disease and any stress imposed by the environment – or for gauging the effectiveness of new health-care measures. SIM could prove invaluable in more efficiently informing and targeting limited health-care resources. Illicit drugs have certainly provided insights for new ways to monitor the health of entire populations.

10 Summary

The published literature that addresses the many facets of pharmaceutical ingredients as environmental contaminants has grown exponentially since the 1990s. Although there are several thousand active ingredients used in medical pharmaceuticals worldwide, illicit drug ingredients (IDIs) have generally been excluded from consideration. Medicinal and illicit drugs have been treated separately in environmental research even though they pose many of the same concerns regarding the potential for both human and ecological exposure. The overview presented here covers the state of knowledge up until mid-2010 regarding the origin, occurrence, fate, and potential for biological effects of IDIs in the environment.

Similarities exist with medical pharmaceuticals, particularly with regard to the basic processes by which these ingredients enter the environment – excretion of unmetabolized residues (including via sweat), bathing, disposal, and manufacturing. The features of illicit drugs that distinguish them from medical pharmaceuticals are discussed. Demarcations between the two are not always clear, and a certain degree of overlap adds additional confusion as to what exactly defines an illicit drug; indeed, medical pharmaceuticals diverted from the legal market or used for non-medicinal purposes are also captured in discussions of illicit drugs. Also needing consideration as part of the universe of IDIs are the numerous adulterants and synthesis impurities often encountered in these very impure preparations. Many of these extraneous chemicals have high biological activity themselves.

In contrast to medical pharmaceuticals, comparatively little is known about the fate and effects of IDIs in the environment. Environmental surveys for IDIs have revealed their presence in sewage wastewaters, raw sewage sludge and processed sludge (biosolids), and drinking water. Nearly nothing is known, however, regarding wildlife exposure to IDIs, especially aquatic exposure such as indicated by bioconcentration in tissues. In contrast to pharmaceuticals, chemical monitoring surveys have revealed the presence of certain IDIs in air and monetary currencies – the latter being of interest for the forensic tracking of money used in drug trafficking. Another unknown with regard to IDIs is the accuracy of current knowledge regarding the complete scope of chemical identities of the numerous types of IDIs in actual use (particularly some of the continually evolving designer drugs new to forensic chemistry) as well as the total quantities being trafficked, consumed, or disposed.

The major aspect unique to the study of IDIs in the environment is making use of their presence in the environment as a tool to obtain better estimates of the collective usage of illicit drugs across entire communities. First proposed in 2001, but under investigation with field applications only since 2005, this new modeling approach for estimating drug usage by monitoring the concentrations of IDIs (or certain unique metabolites) in untreated sewage has potential as an additional source of data to augment or corroborate the information-collection ability of conventional written and oral surveys of drug-user populations. This still evolving monitoring tool has been called “sewer epidemiology” but is referred to in this chapter by a more descriptive proposed term “FEUDS” (Forensic Epidemiology Using Drugs in Sewage). The major limitation of FEUDS surrounds the variables involved at various steps performed in FEUDS calculations. These variables are summarized and span sampling and chemical analysis to the final numeric calculations, which particularly require a better understanding of IDI pharmacokinetics than currently exists. Although little examined in the literature, the potential for abuse of FEUDS as a tool in law enforcement is briefly discussed.

Finally, the growing interest in FEUDS as a methodological approach for estimating collective public usage of illicit drugs points to the feasibility of mining other types of chemical information from sewage. On the horizon is the potential for “sewage information mining” (SIM) as a general approach for measuring a nearly limitless array of biochemical markers that could serve as collective indicators of the specific or general status of public health or disease at the community-wide level. SIM may create the opportunity to view communities from a new perspective – “communities as the patient.” This could potentially lead to the paradigm of combining human and ecological communities as a single patient – as an interconnected whole.

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