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Interaction Between Exposure to Neurotoxicants and Drug Abuse

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1. Introduction

Humans are continuously exposed to a variety of environmental neurotoxicants. Over the past 30 years, at least 100,000 chemicals, including pesticides, food additives, drugs, and cosmetics, have been registered for commercial use in the United States (Muir & Howard, 2006). Twenty years ago, about 750 chemicals had shown neurotoxic effects in laboratory animals (Anger, 1984). Actually, the number is thought to exceed a thousand, although no authoritative estimate of the real number of neurotoxicants is available (Grandjeand & Landrigan, 2006).

About two-thirds of all agricultural use of xenobiotics involves herbicides and about one-eighth involves insecticides; approximately 20% of usage is fungicides, fumigants, and other pesticides (United States Environmental Protection Agency [U.S. EPA], 2001). Organophosphate insecticides represent 50% of all the insecticide use worldwide. In fact in Europe, the use of pesticide on crops exceeds 140.000 metric tons (The use of plant protection products in the European Union. Data 1992–2003. Eurostat statistical books [http://epp.eurostat.ec.europa.eu/cache/ITY_OFFPUB/KS-76-06-669/EN/KS-76-06-669-EN.PDF]). Although European policies to reduce pesticide use have been introduced, according to EU statistical data for 1992-2003, annual pesticide consumption has not decreased. Estimates made by the World Health Organization (WHO) indicate that three million acute organophosphate poisonings and over 200,000 deaths may occur annually in the world (Ferrer & Cabral, 1995; WHO, 1990). Thus, exposure to neurotoxic compounds has become in a serious public health problem worldwide.

Numerous reports have indicated a link between xenobiotic exposure and human health, including disturbances in the CNS (for a review, see Costa et al., 2008). Moreover, numerous studies have reported long-term neurological and neurobehavioral sequelae following a pesticide poisoning event (Delgado et al., 2004; Rosenstock et al., 1991; Steeland et al., 1994). Thus, humans exposed to acute or chronic levels of organophosphate (OP) compounds, a potent neurotoxic widely employed in industry, households and agriculture for pest control, exhibit long-term alterations in neuropsychological performance and cognitive processes, such as processing speed, visual attention, visuoperceptual abilities, memory impairment and problem solving (Farahat et al., 2003; Fiedler et al., 1997; Roldan-Tapia et al., 2004, 2006;

Steenland et al., 1994). Also, emotional deficits have been found after exposure to OPs (Savage et al., 1998; Yokoyama et al., 1998). Pesticide exposure has been correlated with emotional disturbances such as anxiety increases, depression and suicide risk (London et al., 2005; Roldan-Tapia et al., 2006).

On the other hand, the use of pesticides in agriculture has been linked with several dopamine-associated CNS disorders including Parkinson´s Disease (PD) (Dick, 2006) and Attention-Deficit/Hyperactivity Disorder (ADHD) (Bouchard et al., 2010). Specifically, pesticide exposure is a risk factor for PD (Ascherio et al., 2006; Brown et al., 2006; Dick, 2006) and recent studies have shown that it may contribute to ADHD prevalence (Bouchard et al., 2010). Given that dopamine (DA) has been identified as the critical neurotransmitter in the reward circuit mediating substance abuse (for a review, see Di Chiara & Bassareo, 2007), exposure to certain environmental neurotoxicants might influence the development of drug addiction. There are numerous reports associating neurotoxicant exposure and dopaminergic disorders such as PD and ADHD in the literature; however studies examining any potential effects of neurotoxicants on drug addiction are just recently being conducted and published, in spite of the fact that drug abuse is an important public health problem leading to serious negative consequences for individuals and society. Estimates of the total overall costs of substance abuse in the United States, including health- and crime-related costs, exceed $600 billion annually (Office of National Drug Control Policy, 2004). This includes approximately $235 billion for alcohol abuse (Rehm et al., 2009). Thus, these data stresses the need for new scientific research aimed toward the assessment of neurochemical and neurobiological mechanisms underlying exposure to neurotoxicants and drug abuse.

2. Environmental neurotoxicants and drug abuse

In recent years, a growing body of clinical evidence has revealed that acute, intermittent or continuous exposure to a wide variety of chemically unrelated environmental pollutants (such as volatile organic chemicals, woods preservatives, solvents, or organophosphate pesticides) might result in the development of multiple chemical intolerance (Miller, 2001) and increased sensitivity to drugs of abuse (Newlin, 1994; Sorg & Hochstatter, 1999). The general population is exposed to multiple agents, either as intrinsically complex mixtures or as separate substances, such as specifics drugs. Since the behavior of any given chemical in the body is affected by other chemicals, there is a need to study the toxicological and behavioral effects of environmental neurotoxicant mixtures and drugs. Since both environmental neurotoxicants and drug abuse present a health hazard to the population, these studies should merit special attention. Moreover, such studies would open new perspectives to the promising and exciting scientific field that tries to bridge environmental health sciences, toxicology and drug research.

A large variety of studies in animals (Mutti et al., 1988; Von Euler et al., 1991, 1993) and humans (Edling et al., 1997) have demonstrated that repeated volatile organic compound exposure have deleterious effects on the dopaminergic system. The most ubiquitous volatile organic compound is formaldehyde (Form). Acute exposure to formaldehyde can cause eye, nose, throat, and skin irritation, whereas long-term exposure has been linked to certain cancers as well as asthma (Daisey et al., 2003). Furthermore, numerous animal studies on the

adverse effects of formaldehyde on behavioral responses to cocaine have revealed drug-pollutant cross-sensitization (Sorg et al., 1996, 1998, 2001).

In 1996, Sorg and her collaborators demonstrated that animals pretreated with repeated high-level formaldehyde inhalation (1h/day x 7days) showed a significantly enhanced locomotor response to cocaine compared to controls, an indicator that specific limbic pathways may have been sensitized (Sorg et al., 1996). However, the same pattern of exposure, but with low-level formaldehyde doses failed to cause behavioral sensitization to cocaine (Sorg et al., 1998) suggesting that formaldehyde effects on behavioral response to cocaine are dose-dependent.

Paradoxically, long-term low-level formaldehyde exposure (1h/day x 5days/week x 4 weeks) produced behavioral sensitization to later cocaine injection, suggesting altered dopaminergic sensitivity in mesolimbic pathways (Sorg et al., 1998). More specifically, this study has shown that repeated exposure to a relatively low-level volatile organic compound, formaldehyde, amplifies behavioral responses to cocaine. Taking together, these data suggests that the effect of formaldehyde on the cross-sensitization to cocaine depends both on the dose and on the pattern of exposure to this volatile organic compound (Sorg et al., 1998).

Furthermore, humans are routinely exposed to heavy metals through a variety of sources (air, food, water or soil). Thus, prolonged exposure to heavy metals, such as cadmium, copper, lead, nickel, and zinc can cause deleterious health effects in humans (for a review, see Järup, 2003). Mainly, heavy metal exposure can directly influence behavior by impairing mental and neurological function, influencing neurotransmitter production and use, and altering numerous metabolic body processes. The adverse effects of heavy metal exposure are well documented; however, few studies have been carried out to understand their effects on drug use. Next, we are going to describe the effect of two heavy metals (lead and manganese) over the incidence of drug abuse.

The symptoms of acute lead poisoning are headache, irritability, abdominal pain and various symptoms related to the nervous system. Additionally, populations exposed to environments with high lead concentrations may show an increase in the incidence of drug abuse (Ensminger et al., 1997). Experimental studies show that adult lead exposure decreases behavioral sensitivity to cocaine (Burkey et al., 1997; Nation et al., 1996). Animal studies have found evidence that chronic lead exposure in adulthood causes a delay in the development of cocaine-induced locomotor sensitization, as well as a decrease in the magnitude of the locomotor response (Nation et al., 1996). Operant responses, rather than only simple behavioral responses, such as locomotor activity, are also affected by lead exposure. Thus, chronic lead exposure caused cocaine-induced disturbance attenuation in fixed-interval responding (Burkey et al., 1997). In agreement with these data, there are studies showing attenuated cocaine-induced increases in extracellular dopamine levels in the nucleus accumbens region after chronic lead exposure (Nation & Burkey, 1994).

By contrast, the evidence suggests that, after perinatal lead exposure, early developmental lead exposure may increase sensitivity to the reinforcing effects of cocaine and heroin in adulthood (Nation et al., 2004). Several studies have shown that acute administration of cocaine to rats developmentally exposed to low levels of lead produces an attenuation of drug reinforcement according to a conditioned place preference (CPP) paradigm (Miller et

al., 2000), and a drug discrimination preparation (Miller et al., 2001). A similar pattern of attenuation is evident in studies that examined the effects of developmental chronic low-level lead exposure on morphine-induced CPP (Valles et al., 2003). Thus, these studies suggest that lead exposure during development can cause long-term changes in the response that these individuals give to drugs of abuse in adulthood, probably reducing the reinforcing properties of drugs.

Consistent with these data, there is experimental evidence indicating that exposure to another heavy metal, manganese (Mn), has had effects on psychostimulant vulnerability too. Thus, Mn exposure in young adult rats leads to a reduced behavioral response to amphetamines (Vezer et al., 2007). Interestingly, Mn-exposed rats show opposite locomotor responsiveness when challenged with different doses of cocaine (Reichel et al., 2006). Specifically, postnatal Mn exposure causes increased locomotor activity in combination with lower doses of cocaine; and an attenuated locomotor response in combination with high doses of cocaine. These data suggests that Mn exposure can increase dopaminergic receptor sensitivity. In fact, postnatal Mn exposure caused persistent declines in DAT protein expression and [3H] dopamine uptake in the striatum and nucleus accumbens, as well as long-term reductions in striatal dopamine efflux into adulthood (McDougall et al., 2008).

Another set of experiments was carried out to study the effects of pesticides on drug-induced behavior. These studies have shown, for example, that the daily administration of a oral dose of herbicide 2,4-dichlorophenoxyacetic acid (2,4-D) during gestation and development up to post-natal day 23 (PND23) increases an animal's sensitivity to amphetamine (Duffard & Evangelista de Duffard, 2002).

Also, it has been shown that exposure to another pesticide, chlorpyrifos, causes alteration in several drug-induced responses. For example, tolerance to locomotor effects was shown after a dopaminergic agonist challenge with amphetamine 30 days after exposure to CPF (Lopez-Crespo et al., 2007). In a separate study, the motivational and reward properties of amphetamine were decreased in the place preference paradigm months after CPF administration (Sanchez-Santed et al., 2004). Based on these studies, it has been proposed that CPF intoxication may produce long-term hyposensitivity in the dopaminergic system. Recent studies have found that monoamine levels decreased dramatically in the nucleus accumbens 30 days after CPF exposure (Moreno et al., 2008). Other organophosphates, such as chlorphenvinphos, also cause changes in the dopaminergic system. Thus, behavioral studies have shown that 3 weeks after acute exposure to high doses of chlorphenvinphos (CVP), there is an hyposensitivity to behavioral responsiveness to amphetamine and scopolamine (Gralewicz et al., 2000; Lutz et al., 2000, 2005). Furthermore, exposure to chlorphenvinphos prevents behavioral sensitization to amphetamine (Lutz et al., 2006).

3. Environmental neurotoxicants and ethanol intake

As described in the previous section, several studies have shown the interaction between neurotoxicants and the abuse of certain drugs, such as cocaine, amphetamines or morphine. Given that ethanol (EtOH) is one of the most commonly used drugs worldwide, next we will present the specific literature referring to neurotoxicant exposure and its relationship to ethanol intake.

The great majority of people in modern society regularly consume ethanol. In fact, about 100 billion Euros on alcoholic beverages are spent annually by Europeans, which is reflected by the high rate of alcohol consumption per capita of 10 liters of pure ethanol per year. But, consuming and abusing these huge amounts of alcohol is clearly a problem, with enormous health and socioeconomic effects worldwide. According to the Alcohol-Related Disease Impact (ARDI) tool, from 2001–2005, there were approximately 79,000 deaths annually attributable to excessive alcohol use. Thus, excessive alcohol use is the 3rd leading lifestyle-related cause of death for people in the United States, after tobacco addiction and obesity (McGinnis & Foege, 1999). The economic cost of ethanol abuse is estimated at greater than $235 billion every year (Rehm et al., 2009), including health care costs, lost worker productivity, and crime.

Several studies have suggested a relationship between several neurotoxic agents and alcohol intake. First of all, we will focus on the interaction between lead exposure and alcohol intake. The exposure to this heavy metal has already been linked to reduced behavioral sensitivity to cocaine (Burkey et al., 1997; Nation et al., 1996). Also, populations exposed to environments with high lead concentrations may show an increase in the incidence of drug abuse (Ensminger et al., 1997). Epidemiological data has revealed that alcoholic industrial workers have higher blood lead levels than their non alcoholic colleagues, suggesting that alcoholic workers could be more susceptible to the toxic effects of lead (Cezard et al., 1992; Dalley et al., 1989).

Animal studies have found evidence that ethanol exposure for 8 weeks resulted in a marked increase in the accumulation of lead in the blood (Gupta & Gill, 2000a) and brain (Gupta & Gill, 2000b) of animals exposed to lead, making them more vulnerable to the toxic effects of lead. Thus, for example, levels of lead in the brain were approximately twice higher in lead and ethanol co-exposed animals than in animals exposed to lead alone (Gupta & Gill, 2000b). Another set of experimental studies has shown that mice treated chronically with lead exhibit some alterations in ethanol-induced behaviours, such as a reduction in ethanol-induced locomotor activity (Correa et al., 1999). In a self-administration task, dietary lead exposure led to lever pressing at a significantly lower rate than the control group (Nation et al., 1991). Apparently, lead toxicity reduces sensitivity to ethanol effects. Moreover, when subjects were exposed simultaneously to lead and ethanol, the level of dopamine decreased significantly, and was accompanied with increased norepinephrine levels (Flora & Tandom, 1987; Gupta & Gill, 2000b).

As with lead, simultaneous exposure to aluminium and ethanol also deplete brain dopamine (DA) and 5-hydroxytryptamine (5-HT) levels, when compared to rats given aluminium alone (Flora et al., 1991). Also, the concentration of aluminium in the blood and liver was significantly higher in rats exposed to both aluminium and ethanol than in those exposed only to aluminium. These results suggest that prolonged ethanol consumption may increase the rats' susceptibility to certain effects of aluminium.

3.1 The relationship between organophosphate exposure and ethanol intake

Decades ago, an interesting study showed that 114 agricultural workers suffering acute organophosphate intoxication developed intolerance to nicotine- and ethanol-containing beverages (Tabershaw & Cooper, 1966). Another epidemiological study, carried out by

Spiegelberg in 1961, described persistent intolerances for alcohol and nicotine among Germans who had manufactured chemical weapons, including organophosphate nerve agent, during World War II (Spiegelberg, 1961). These studies were the first to propose the existence of a relationship between organophosphate compound exposure and ethanol intake. In addition, more recently, clinical reports have shown that a significant percentage (66%) of Gulf War veterans reported that alcohol beverages, even a can of beer, made them feel ill (Miller, 2001). Unfortunately, there are not many epidemiological studies considering organophosphate exposure as a determinant of ethanol intake.

In agreement with clinical data, Overstreet and his colleges reported that Flinder rats, which had been bred for increased sensitivity to organophosphate poisoning, showed enhanced responses to ethanol or nicotine (Overstreet et al., 1996, 2001). Thus, Flinder Sensitive Line (FSL) rats exhibited a significantly greater ethanol-induced (Overstreet et al, 1990, 1996) and nicotine-induced hypothermic response (Overstreet et al, 1996; Schiller & Overstreet, 1993) compared to its parallel bred counterparts, the Flinder Resistant Line (FRL) rats. It suggests that FSL rats, selectively bred for increased cholinergic responses, also show an increased sensitivity to the effects of alcohol or nicotine.

Taken together, clinical and experimental evidence strongly points to the existence of important, but poorly understood, neurobiological interactions between organophosphate exposure and ethanol intake. Therefore, we investigated the impact of OP exposure on voluntary alcohol consumption from a molecular and a behavioral approach in an animal model. To that aim, we employed an experimental model in Wistar rats based on the administration of a single high dose (250 mg / kg) of the organophosphate chlorpyrifos (CPF). CPF is an OP used worldwide in the agricultural industry and in households as a pesticide (Pope, 1999; Richardson, 1995). The primary mechanism of acute toxic action of these compounds is acetylcholinesterase (AChE) inhibition, which results in acute cholinergic over stimulation at nicotine and muscarinic synapses of the peripheral, autonomic and central nervous system (Lotti, 2001; Richardson, 1995). Additionally, non-AChE targets such as the monoaminergic (Aldridge et al., 2003; Dam et al., 1999; Moreno et al., 2008), the gabaergic (Rocha et al., 1996; Sánchez-Amate et al., 2002), or the glutamatergic systems (Gultekin et al., 2007) have also been proposed as alternative mechanisms involved in the acute lethal action and/or side effects of short and long-term OP exposure.

After subcutaneous administration, CPF keeps acetylcholinesterase (AChE) activity mildly inhibited for weeks. This unique biochemical profile points to the long-lasting presence of the compound in the body (Bushnell et al., 1993; Pope et al., 1992). Since CPF-induced AChE inhibition is not associated with overt cholinergic toxicity (Bushnell et al., 1993; Pope et al., 1992), exposure to high doses of this OP has been used in animal research to investigate the neurobehavioral effects of OP exposure during a wide temporal window of approximately 8-12 weeks (Richardson, 1995). Thus, exposure to a single subcutaneous injection of CPF would provide an animal model to conduct extensive neurobehavioral testing during a long interval of approximately 8 weeks.

The two-bottle choice paradigm provides a convenient method for a rapid screening of alcohol preferences in rats. Thus, early paradigms assessing the reinforcing effects of alcohol typically used an oral preference paradigm where animals were allowed to drink alcohol or water. In fact, free choice procedures are widely employed for selection of rat lines with genetically determined high or low ethanol preference (Files et al., 1997; Sinclair et al., 1989).

Eight weeks after CPF administration, Wistar rats were allowed to drink ethanol in a two bottle paradigm (water vs. 8%-20% w/v ethanol) to evaluate if pre-exposure to the organophosphate caused them long-lasting avoidance. In this long-term drinking model, changes in alcohol-drinking behavior occur over time between CPF and vehicle-treated rats. Thus, the CPF pretreated rats showed lower ethanol consumption and ethanol preference than the control group at 8, 15, and 20% ethanol concentration (Carvajal et al., 2007). These results are consistent with clinical and experimental data showing that exposure to organophosphates might be linked to increased ethanol sensitivity and reduced voluntary consumption of ethanol-containing beverages in humans.

Since different factors might contribute to alcohol consumption, from week 4 to week 8 after CPF administration, an additional set of neurobiological, physiological, and behavioral responses to ethanol were evaluated. First, we analyzed whether CPF alters gustatory sensory processing as measured by taste preferences for sucrose, quinine and saccharin. CPF-pretreated rats showed the same taste preference pattern as vehicle-treated rats. Secondly, we verified that ethanol avoidance was not secondary to ethanol-induced flavor aversion disturbances since both CPF- and vehicle-treated rats showed a similar pattern of flavor avoidance in response to ethanol. Finally, we explored the sedative/hypnotic properties of alcohol as assessed by the righting reflex. These data showed that 4 weeks after poisoning, CPF-treated rats showed enhanced sensitivity to the sedative properties of ethanol not associated with altered blood ethanol levels.

It is possible that increased ethanol sensitivity is partially mediated by several CPF toxicity mechanisms (for more details, see Carvajal et al., 2007). As noted above, the main CPF action mechanism is acetylcholinesterase inhibition. For example, it was demonstrated that administering cholinesterase inhibitors, galantamine or desoxypeganine, reduces alcohol consumption in alcohol-preferring rats (Doetkotte et al., 2005; Mann et al., 2006). Also, CPF decreases nicotinic alpha-7nAch receptor density (Slotkin et al., 2004), with a known role in ethanol intake and ethanol-induced sedation (Bowers et al., 2005; de Fiebre and de Fiebre, 2005). In this regard, there have been significant studies showing, at least at the genetic level, that knockout mice lacking alpha-7nAchR receptor specifically show reduced ethanol intake and increased sedation to ethanol (Bowers et al., 2005; de Fiebre and de Fiebre, 2005). Finally, alternative noncholinesterasic CPF neurotoxicity mechanisms (Casida and Quistad, 2004) might also cause ethanol avoidance (for more details, see Carvajal et al., 2007). However, future experimental research is required to test more specifically the implication of these CPF toxicity mechanisms in ethanol avoidance.

In summary, administration of a single high dose of CPF to adult Wistar rats elicited long-lasting reduced voluntary ethanol drinking and increased sedation to ethanol without evidence of altered ethanol metabolism, which indicates that CPF-ethanol neurobiological interactions may exist. Thus, there is the interesting possibility that some OPs such as CPF might induce long-lasting neural disturbances in brain systems critically involved in neurobehavioral responses to ethanol.

Investigating specific brain targets has been proposed as an important tool for developing our understanding of behavioral, emotional and cognitive impairments caused by OP compounds (Gupta, 2004). Considering this, in another study we explore whether CPF exposure induces significant disturbances in basal and/or ethanol-evoked neural activity in

a set of cholinoceptive brain regions critically involved with neurobiological responses to ethanol. For this purpose, brain regional c-fos expression in response to acute ethanol (1.5 or 3.0 g/kg, i.p.) or saline solution was assessed in adult male Wistar rats previously injected with either a single high dose of CPF (250 mg/kg, sc) or vehicle. Results showed that first, CPF exposure did not modify the regional c-fos expression in response to acute ethanol administration; and secondly, CPF administration reduces long-term basal c-fos expression in the arcuate hypothalamic nucleus.

The arcuate hypothalamic nucleus AgRP/NPY expressing cells have been hypothesized to have a key role in voluntary ethanol consumption (Kalra & Kalra, 2004; Thiele et al., 2003). Taking together this fact and the present observation that long-term CPF exposure blunts c-fos expression in this brain region, one tempting hypothesis is that CPF causes long-term inhibition of neural activity in AgRP/NPY expressing cells in the Arc leading to reduced voluntary ethanol consumption. However, future behavioral and molecular studies are required to understand more extensively the role of Arc neural disturbances in long-term and long-lasting CPF-induced ethanol avoidance.

Although experimental data shown here constitute only an initial exploration of the putative relationship between organophosphate exposure and ethanol intake, both preclinical and experimental literature, and the preliminary findings of this study, suggests that further research is warranted. The use of well controlled animal models aiming to characterize the neurobiological mechanisms of drug/pollutant interactions would open new perspectives to this new scientific field that bridges environmental health sciences, toxicology, and drug research (Miller, 2001). Also, such research may result in public health and prevention programs that produce significant improvements in the integrity of long-term cognitive and behavioral outcomes.

4. Conclusion

In this chapter, we have provided a brief overview of this new scientific field that bridges environmental health sciences, toxicology, and drug research. In recent years, a large variety of studies have shown that different environmental neurotoxicants can lead to vulnerability to drug abuse. However, neurobiological interactions between environmental pollutants and drugs of abuse are still poorly understood. In the particular case of pesticides, both clinical and experimental research have shown that exposure to organophosphates might be linked to increased ethanol sensitivity and reduced voluntary consumption of ethanol-containing beverages. However, the mechanisms by which organophosphates may exert their effects on ethanol intake have yet to be elucidated. Accordingly, further laboratory and epidemiological research into the role of pesticides, and specifically chlorpyrifos, exposure in alcohol intake is needed. These studies appear to demonstrate a link between environmental neurotoxicant exposure and drug addiction, although much work needs to be done to further identify and characterize the underlying mechanisms involved.

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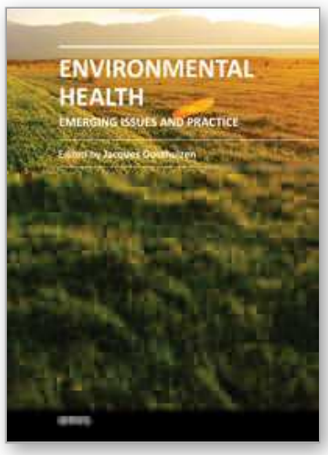

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Environmental health practitioners worldwide are frequently presented with issues that require further investigating and acting upon so that exposed populations can be protected from ill-health consequences. These environmental factors can be broadly classified according to their relation to air, water or food contamination. However, there are also work-related, occupational health exposures that need to be considered as a subset of this dynamic academic field. This book presents a review of the current practice and emerging research in the three broadly defined domains, but also provides reference for new emerging technologies, health effects associated with particular exposures and environmental justice issues. The contributing authors themselves display a range of backgrounds and they present a developing as well as a developed world perspective. This book will assist environmental health professionals to develop best practice protocols for monitoring a range of environmental exposure scenarios.

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