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Flame retardants

Persistent pollutants in land-applied sludges

Disposal of sewage sludge by application to agricultural and other land is widely practised and is presumed to be environmentally beneficial, but we have found high concentrations of an environmentally persistent class of organic pollutants, brominated diphenyl ethers (BDEs), in 'biosolids' from four different regions of the United States. These compounds are widely used as flame retardants, and their presence suggests that the environmental consequences of land application of biosolids need further investigation. We also frequently detected BDEs in wild-caught fish, indicating another pathway for human exposure.

Over half of the sewage sludge produced annually in the United States is applied to land, amounting to roughly 4 million tons in 1998 (ref. 1). Sludges are treated before application to reduce odour and pathogen content and their metal burden is regulated. But attention has focused less on persistent organic pollutants since usage of the most notorious (for example, polychlorinated biphenyls) has decreased and pretreatment of industrial waste water has improved[1,2].

We analysed 11 biosolid samples before land application from Virginia, Maryland, New York state and California, and found that they all contained high concentrations of BDEs. These flame-retardant polymers are structurally similar to polybrominated biphenyls, the use of which was curtailed after a significant contamination incident in 1973 involving livestock feed in Michigan[3].

However, global consumption of BDEs continues to increase, reaching 67,125 metric tonnes in 1999 (refs 4, 5). The most bio-accumulative and toxic BDEs (those containing 4–6 bromine atoms) are being increasingly detected in humans and wildlife from both developed and remote areas[5–7]. These were present in significant amounts in the biosolids we examined and their relative contributions matched those in 'Penta', the commercial formulation used as a flame retardant in polyurethane foam (Fig. 1). North America accounts for about 98% of global demand for Penta, estimated at 8,290 tonnes in 1999 (ref. 4).

How BDEs are released from polymers has been uncertain, as these applications are considered to be non-dispersive[7]. However, breakdown of discarded polyurethane foam, which may contain up to 30% Penta by weight[5], may contribute to this. We found that the surface of foam became brittle and sloughed off after 4 weeks of exposure to ambient summer conditions. The particles generated are easily transported and the polymer matrix preserves the formulation's original BDE composition.

The total concentration of Penta-like BDEs in these biosolids was 1,100–2,290 μg per kg dry weight, suggesting that input was high and consistent, regardless of the region of origin and irrespective of pre-application treatment (see supplementary information). Concentrations exceed those in European sludges by 10- to 100-fold[8], which is commensurate with the greater demand for Penta in the United States. The European Commission recently proposed a ban on the use of Penta, on the basis of its reported exponential increase in human breast milk and perceived health risks[9].

The fully brominated Deca product constitutes 82% of the total global BDE market[4]. It is rarely reported in wildlife, perhaps because of its low bioavailability. Deca consists principally of a single BDE (BDE-209) and is used to curtail fires in textiles and in relatively stable, rigid polymers, such as those used in television and computer casings[5]. Unlike those of Penta constituents, BDE-209 concentrations varied widely among the biosolids we analysed (84.8–4,890 μg kg^{-1}; see supplementary information). Although there is little evidence for the degradation of Deca to Penta-like compounds, some photolysis of Deca to less brominated diphenyl ethers is possible[5,7].

We also detected BDEs in 87% of fish sampled from Virginia waters (quantification limit in fillets, 5 μg per kg lipid; $n = 334$). The principal Penta constituents (BDE-47, -100 and -99) predominated in these samples (Fig. 1). This finding indicates that significant environmental release of these pollutants is occurring in the United States and that humans may be exposed to them through their diet. Carp from one Virginia stream contained 47,900 μg kg^{-1} of total BDEs, rivalling the highest fillet

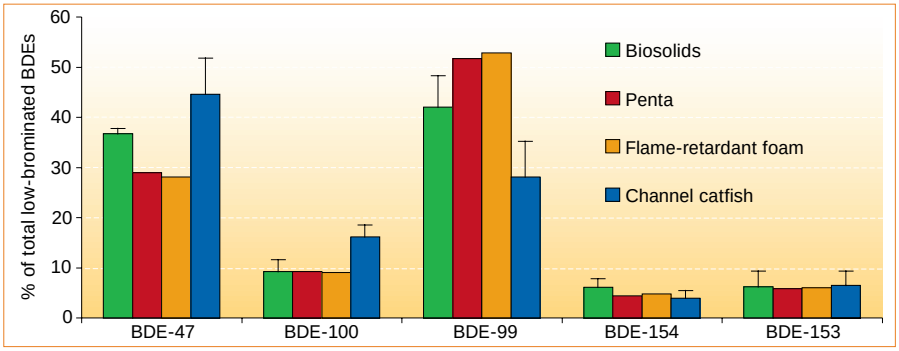

Figure 1 Brominated diphenyl ethers (BDEs) are produced commercially and occur in the environment as mixtures of compounds of varying bromination. Relative contributions of tetra- (BDE-47), penta- (BDE-100 and -99) and hexa- (BDE-154 and -53) brominated versions were similar in 11 biosolids obtained from four different regions of the United States, in the Penta commercial product (used as a flame retardant in polyurethane foam), in treated foam and in wild-caught fish (data shown are for 15 composite samples of channel catfish, *Ictalurus punctatus*, an omnivorous bottom-dwelling species) collected from Virginia lakes and rivers (error bars represent standard deviation). BDE-209 was not detected in fish but was present in biosolids.

burdens reported in the world so far[4].

These compounds are also detectable in urban and rural air[10], indicating the potential for long-distance atmospheric transport. It seems that BDEs are an important — but generally unrecognized — persistent organic pollutant in the United States. Extensive use of Penta and the high burden of BDEs in land-applied biosolids may facilitate environmental dissemination of less-brominated BDEs both locally and globally.

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Neuroadaptation

Incubation of cocaine craving after withdrawal

Relapse to cocaine addiction is frequently associated with subjective reports of craving, a poorly understood state that precedes and accompanies cocaine-seeking behaviours[1]. It has been suggested[2] that over the first few weeks of withdrawal from cocaine, human addicts become sensitized to drug-associated environmental cues that act as external stimuli for craving, although the evidence for this is inconsistent[3]. Here we provide behavioural evidence from laboratory animals suggesting that the onset of craving is delayed and that craving does not decay, but rather increases progressively, over a two-month withdrawal period.

We modelled cocaine-craving behaviour by using rats trained to press a lever to receive an intravenous injection of cocaine and then testing them under conditions in which lever-pressing could continue but the cocaine reward was no longer given. In this model, lever-pressing drops to almost zero ('extinguishes') but can be temporarily reinstated by giving the animal an unearned 'priming' injection of the drug[4], by administering some forms of stress[5], or by presenting drug-associated cues[6] — factors that are known to provoke drug craving in human addicts[1,7,8].

We trained seven groups of rats to press the lever for intravenous cocaine injection (0.5 mg per kg body weight per lever-press). Individual rats lived in a chamber that had a retractable lever. Each training session began with insertion of the lever and illumination of a red house light. At the end of each session, the house light was turned off and the lever retracted. A 5-second tone–light signal accompanied each earned injection. After 10 days of 3-hour training sessions twice daily, in which the animals came to earn 55.3 ± 2.7 infusions per day, they were withdrawn from cocaine for 1, 2, 4, 7, 15, 29 or 60 days. During the withdrawal period, the lever was retracted and the house light was kept off.

We subsequently tested each group under two extinction conditions in which cocaine reward was withheld. First, we assessed resistance to extinction in the presence of the house light and the lever — cues that during training had indicated drug availability — but in the absence of the light and tone that were previously paired with drug injection. The animals were allowed to lever-press for six to eight 1-hour sessions (separated by 5-min intervals, during which the lever was retracted and the house light turned out) until their response fell to less than 15 presses per session. We found that lever-pressing was minimal in rats that had been deprived of cocaine for a single day and maximal in animals that had been deprived for 60 days (Fig. 1a).

The second test of cocaine seeking was a cue-induced reinstatement test conducted 5 min after the last of the extinction sessions. This test began with a 5-second presentation of the tone–light signal that had previously accompanied cocaine injection; each lever-press in this test resulted in another presentation of the tone–light signal[6]. In this test, the animals were not only exposed to the cues that would normally signal cocaine availability, but they were also exposed to the conditioned reinforcing cues that previously confirmed cocaine reward. Again, response was minimal after a single day of cocaine deprivation and maximal after 60 days (Fig. 1b). We found a linear increase over 2 months of cocaine withdrawal in the rats' sensitivity to similar drug-associated environmental cues that stimulate cocaine craving in humans[1].

Our results are consistent with clinical observations in humans[2] and suggest that a delayed-onset craving syndrome develops or 'incubates' during the first 2 months of cocaine abstinence, and probably lasts for longer. Although the mechanisms responsible for this incubation are not known, the intensification of cocaine seeking described here develops over a period when most of the neuroadaptations that accompany withdrawal from chronic cocaine addiction are in progressive decline[9–11].

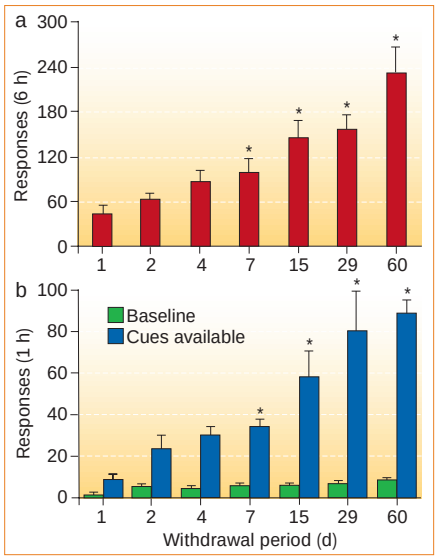

Figure 1 Persistence of a cocaine-seeking habit as a function of time since the last day of self-administration of cocaine. **a,** Mean (± standard error) number of non-reinforced responses on the lever previously associated with cocaine, from six extinction sessions in the presence of the house light and lever cues that were previously associated with cocaine availability. **b,** Mean (± standard error) number of non-reinforced responses on the lever previously associated with cocaine in the subsequent presence of the light–tone signal (conditioned reinforcer) that was previously associated with earned cocaine injections. Baseline data are from the previous extinction session. *Different from day 1 ($P < 0.01$).

The time course of this intensified drug seeking is similar to that of psychostimulant sensitization, which becomes progressively stronger with increasing abstinence for periods of up to several weeks[12,13]. Whatever the mechanism by which craving is incubated, our evidence is inconsistent with the view that cocaine craving decays progressively after cessation of drug use. It suggests instead that the individual is most vulnerable to relapse at times well beyond the acute phase of drug withdrawal.

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