

Neurobehavioral toxicity of methylmercury and PCBs Effects-profiles and sensitive populations

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Abstract

A large and growing body of literature is available on the neurotoxicity of methylmercury and PCBs as expressed in the behavior of both humans and laboratory animals. Methylmercury and PCBs will be compared with PCBs with attention directed at overlaps and distinctions in their profiles of neurotoxicity. It is possible with methylmercury and, to a lesser extent, with PCBs to characterize the sensory, motor, and cognitive consequences of exposure. Methylmercury is emerging as a life-span developmental neurotoxicant: adverse effects of exposure have been identified in development and during aging in human populations as well as in laboratory animals. Less is known about the PCBs on this count. While the mechanisms of neurotoxicity are not understood for either class of compounds, emerging clues are pointing to the possibility of overlap in some mechanisms of neurotoxicity. © 2002 Elsevier Science B.V. All rights reserved.

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1. Introduction

Studies of laboratory animals and of human populations both contribute to our understanding of the neurotoxicity of any compound. Epidemiological investigations of human populations carry the distinct advantage that they are conducted on the population of interest. However, they also carry with them the burden of being correlational in nature and of having little control, even under the best of circumstances, over the characteristics of exposure or of the population (Committee on Environmental Epidemiology of the National Research Council, 1991; Needleman, 1986). Studies of laboratory animals greatly facilitate conclusions about causal relationships between exposure and effect and can uncover mechanisms of action, in part because they provide greater control over exposure and such characteristics of the subjects such as housing, diet, and exposure to other agents.

Behavioral studies are a necessary component of any investigation of neurotoxicants. These studies can provide basic screening information about the relationship

between overtly toxic or lethal doses and the dose at which some behavioral effects appear. Such studies can also be useful in the early stages of investigation by identifying functional domains that a neurotoxicant affects (Moser, 1989; Moser and MacPhail, 1990).

Behavioral studies offer much more than screening information, however. Advanced applications focus on functional domains, such as motor function, sensory function, schedule-controlled behavior, memory and learning that might be especially sensitive to a particular neurotoxicant. These point to mechanisms of action, or can support implications of hazard that might be based on neuropathologic, neurochemical, or physiological actions of chemicals. As such information is acquired, the picture linking brain-behavior relationships and the actions of neurotoxicants comes into sharper focus.

In this paper the neurotoxicity of methylmercury and PCBs is examined in light of variables that modify the neurotoxicity of these compounds. The neurotoxicity associated with methylmercury and PCBs are briefly reviewed and then human and animal studies suggesting that methylmercury's neurotoxicity can be exacerbated by the presence of PCBs and unmasked by age are reviewed.

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2. Structural relationships

The PCBs constitute a class of 209 compounds of varying toxicity. Structure–activity relationships have been drawn based on binding to the Ah receptor, number and location of chlorine atoms, and planarity of the molecule (Chauhan et al., 2000; Kodavanti and Tilson, 1997; Safe, 1990; Shain et al., 1991). Relationships between the planarity of the PCB molecule and the profile of effects will be reviewed below. Methylmercury bears no structural resemblance to PCBs but methylmercury and the PCBs frequently co-exist in fish and it is largely for this reason that these neurotoxicants can be considered together. There is a more fundamental reason for considering these together. Recent evidence suggests that methylmercury and PCB mixtures may interact synergistically, despite structural differences, when present together (Bemis and Seegal, 1999).

The presence of PCBs and methylmercury in similar media coupled with their potential for interaction indicate that their neurotoxicity profiles should be compared. This becomes especially important when attempting to predict adverse effects in populations, such as those around the Great Lakes, that consume fish contaminated with PCBs and methylmercury.

3. Effects profiles

3.1. Methylmercury

Methylmercury is the form of mercury that presents the major risk to populations. Methylmercury is readily taken up by the gut and crosses the blood–brain barrier passively, because of its lipid solubility, and actively after forming a complex with cysteine and carried across the barrier by a methionine transporter (Aschner and Aschner, 1990). Once in the central nervous system, methylmercury is demethylated and persists (Vahter et al., 1994, 1995).

In animal studies and in many studies of human exposures, methylmercury has been linked most closely with deficits in sensory and motor function. Methylmercury exposure affects the visual, auditory, and somatosensory systems (Merigan, 1980; Rice, 1996b) effects consistent with a cortical basis and consistent with methylmercury's pathology (Berlin et al., 1975; Chang and Annau, 1984; Sato and Nakamura, 1991). The pattern of sensory effects is critically dependent on the age and timing of exposure, as is exemplified in the visual system. Methylmercury exposure during adulthood produces a progressive and irreversible constriction of the visual field (Merigan, 1980), a pattern of toxicity not associated with developmental exposures. Methylmercury exposure during gestation or lactation affects higher-order visual function, as can be seen using

analyses of contrast sensitivity functions taken under conditions of high and low illumination (Rice and Gilbert, 1982, 1990). This technique reveals profound deficits in the ability to extract details as well as integrate visual information into broader shapes. The deficits were associated with developmental exposure to methylmercury, and this was especially evident under less-than-ideal viewing conditions such as poor contrast between regions, vague edges, or poor illumination.

Developmental exposure to methylmercury also affects the development of monkeys' ability to recognize familiar faces (Gunderson et al., 1988). In a series of experiments, Gunderson et al. showed young monkeys photographs of monkey faces. As with children, novel faces elicited longer viewing times than familiar ones in controls. Methylmercury-exposed monkeys looked at familiar faces with longer viewing times than unexposed monkeys, suggesting that these faces did not look familiar, even though they had been seen previously. These deficits might be related to memory deficits (Gunderson et al., 1988) or alternatively to developmental delays or even to visual deficits that impair the exposed monkeys' ability to identify faces, as suggested elsewhere (Newland and Paletz, 2000).

Somatosensory (Rice and Gilbert, 1995) and auditory (Rice and Gilbert, 1992) deficits have also been associated with developmental exposure to methylmercury. In the former, methylmercury-exposed monkeys showed somatosensory deficits that could impair the detection of textures or that could provide proprioceptive feedback required for fine-motor control. Auditory impairments involved losses as great as a full octave in high-frequency hearing.

Clinical evidence of damage to motor systems, including nystagmus, which is indicative of cerebellar damage, and cerebral palsy, which suggests cortical damage, were among the first associated with methylmercury exposure in the Minamata episode (Harada, 1995). In a study conducted in Iraq, the most sensitive indicator of developmental exposure was the appearance of delays in the onset of walking by children (Cox et al., 1989). In animal studies methylmercury appears to impair motor control (Elsner, 1991), and swimming speed (Elsner et al., 1988). Reports that methylmercury may alter the acquisition of high-rate behavior (Bornhausen et al., 1980) were not replicated (Rasmussen and Newland, 1999) but in other studies, this endpoint was used to reveal sensitivity to drug challenges or to aging, and these are described below (Newland and Rasmussen, 2000; Rasmussen and Newland, 2001).

Behavior under a fixed-interval schedule of reinforcement, a useful laboratory preparation for characterizing toxicant effects, is affected by developmental exposure to methylmercury. Under a fixed-interval schedule, the first response after a period of time has elapsed is followed by a reinforcer. The schedule typically engen-

ders a temporally modulated pattern of behavior in which there is a low response rate early in the interval and a high rate late in the interval. In methylmercury-exposed monkeys, an earlier onset of responding in the fixed-interval was noted but response-bursting, a pattern associated with lead and with certain PCBs, was absent (Gilbert et al., 1996; Newland and Paletz, 2000). In rats, methylmercury exposure did not appear to affect behavior under differential-reinforcement of low-rate behavior (Eccles and Annau, 1982), a schedule that explicitly reinforces a temporal structure in behavior since it requires that two responses be separated by a specified inter-response time in order to be eligible for reinforcement.

Methylmercury does not appear to degrade performance on the sorts of discrimination-learning and memory tasks that are commonly associated with cognitive function. Memory in monkeys, as evaluated under delayed alternation procedures, was not impaired by developmental exposure to methylmercury; in fact, the number of errors was smaller in the exposed monkeys under some conditions (Gilbert et al., 1993). In another study, also using primates, a discrimination reversal task that taps the monkeys' ability to acquire discriminations, was also unaffected by developmental exposure to methylmercury (Rice, 1992).

While methylmercury exposure does not disrupt tasks that involve discrimination or memory, which may tap similar processes (Davison and Nevin, 1999; White and Wixted, 1999), methylmercury may affect tasks that involve changes in response–reinforcer relationships. In one study (Newland et al., 1994), squirrel monkeys could press one of two levers for food reinforcement under a concurrent schedule of reinforcement. In this arrangement, one lever provided reinforcement at a higher rate than the other and control monkeys spent more time pressing the richer lever. The relative time spent responding on a lever approximated the relative density of reinforcement derived from that lever for controls, as is commonly seen with this schedule of reinforcement. Exposed monkeys showed a profound response bias reflecting little sensitivity to the source of reinforcement. The effects became especially strong during transition states, when the reinforcement rates associated with the two levers were changed. For example, if the left lever produced a higher reinforcer rate than the right lever, then this relationship was reversed and behavior was tracked as behavior adjusted to the new reinforcement contingencies (Fig. 1). The methylmercury monkeys showed profound disruptions of the transitions. Other investigators have reported impaired acquisition of avoidance tasks (Eccles and Annau, 1982; Hughes and Annau, 1976).

Operant behavior, which is any behavior sensitive to its consequences, is the outcome of a response–reinforcer relationship that takes place in a context. Both

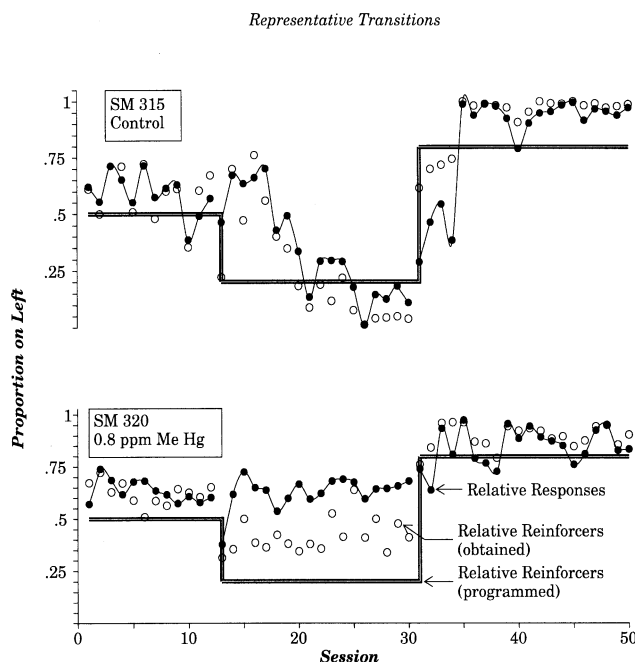


Fig. 1. Representative transitions for a control monkey and one exposed to methylmercury during gestation (adapted from Newland and Reile, 1999; Newland et al., 1994). Symbols represent summaries of performance for individual 30-min sessions. Relative response rate and obtained and programmed reinforcement rates are shown for two transitions. In the top panel the change in behavior and obtained reinforcement rates lagged programmed rates by 4, 30-min sessions. For the exposed monkey, behavior showed little sensitivity to programmed or obtained reinforcement rates during the first transition.

reinforcement processes and discrimination processes play a role in all operant behavior, but certain tasks place differential emphases on contextual or reinforcer control over behavior. Discrimination and memory tasks emphasize the role of the context while most applications of concurrent schedules place a stronger emphasis on reinforcement processes (Davison and McCarthy, 1988; Davison and Nevin, 1999). These different aspects of behavior may also reflect the activity of different neural structures or neurochemical pathways (Donahoe et al., 1993). Mesolimbic dopamine pathways, for example, participate in the strengthening of behavior by reinforcing stimuli (Wise, 1996; Wise and Rompre, 1989) even as it appears that these pathways are independent of emotions or pleasure sometimes associated with reinforcers (Berridge and Robinson, 1998). They also participate in the forming of associations required for a stimulus or a context to occasion the responses that reinforcers strengthen, but they do so through their involvement with other pathways (Donahoe et al., 1993; Spanagel and Weiss, 1999). It may be that discrimination-based tasks are insensitive to methylmercury exposure but tasks that emphasize the acquisition of response–reinforcer relationships might be sensitive to this neurotoxicant (see also Newland and

Paletz, 2000). Experiments with behaving animals in which developmental exposure to methylmercury enhances sensitivity to drugs that alter catecholamine function (Cagiano et al., 1990; Rasmussen and Newland, 2001) suggest a hypothesis that methylmercury alters behavior, at least in part, through its actions on dopamine pathways. Insofar as the development of response–reinforcer relationships is mediated by dopamine pathways, this hypothesis could be extended to speculate that methylmercury's disruption of transitions with concurrent schedules or other response acquisition tasks are mediated similarly, but this suggestion must be treated as speculation at present.

3.2. PCBs

The PCBs constitute a collection of 209 different chlorinated biphenyls that appear in the environment as mixtures of different congeners. Research into the neurotoxic effects of PCBs has been guided by a hypothesis that PCBs forming a coplanar structure resembling the TCDD ('dioxin') molecule have biological effects resembling those of TCDD. Other PCBs do not form a coplanar structure because of steric forces resulting from the location of chlorine atoms. These non-coplanar PCBs have behavioral and neurochemical effects that differ from TCDD and the coplanar PCBs but resemble each other (Newland and Paletz, 2000; Schantz, 1999; Seegal, 1995; Shain et al., 1991).

The structural distinction that divides PCBs into coplanar and non-coplanar compounds corresponds also to functional effects and this distinction may, in turn, reflect binding affinity of these classes to different receptor types. The coplanar PCBs bind preferentially to the Ah receptor, as does TCDD. The potency of coplanar PCBs can be related to TCDD by Toxic Equivalency Factors, which describe the degree to which a particular congener binds to the Ah receptor (Safe, 1990; Van den Berg et al., 1998). The magnitude of the toxic equivalency factor, which can vary over several orders of magnitude for different congeners, is influenced by many factors, including the location of chlorine around the two phenyl rings making up the PCB molecule (Chauhan et al., 2000; Kodavanti and Tilson, 1997; Safe, 1990). The toxic equivalency factor has been related to the behavioral effects of the coplanar PCBs (Newland and Paletz, 2000).

Non-coplanar PCBs do not bind the Ah receptor effectively and the toxic equivalency factors do a poor job of predicting their neurotoxicity (Newland and Paletz, 2000; Schantz, 1999). It is less clear where they do bind, but several lines of evidence point to their disruption of neurotransmitter function, perhaps by altering calcium homeostasis or the initiation or termination of catecholamine neurotransmission. (Schantz et al., 1997; Seegal, 1995; Seegal et al., 1991; Shain et al.,

1991; Tilson and Kodavanti, 1998). These proposed mechanisms are not mutually exclusive.

The coplanar, 'dioxin-like,' PCBs and the non-coplanar PCBs have different profiles of effects, at least in animal studies. There is evidence that the coplanar compounds have effects on simple tests of motor function. These include catalepsy (Hany et al., 1999), performance on a rotating rod and the development of the righting reflex (Thiel et al., 1994). A detailed investigation of gestational exposure to TCDD provides further evidence of motor effects and suggests that these effects may be unrelated to estrogen function (Markowski et al., 2001). Rats exposed to TCDD during gestation pressed a lever for an opportunity to run in a custom-made running wheel that permitted the quantification of coordinated running. TCDD-exposed rats ran less often and had greater difficulty placing their feet on rods used to propel the wheel. The absence of a relationship to estrous cycle suggested that endocrine function was not directly related to this effect but the authors suggested that midbrain monoamine function could play a role in the effects that they reported.

The coplanar compounds also alter the acquisition of avoidance tasks (Hany et al., 1999), behavior under a concurrent schedule of reinforcement (Rice and Hayward, 1999) and performance on a radial arm maze, a spatial learning task (Schantz et al., 1996; Seo et al., 1999) (reviewed in Newland and Paletz, 2000; Schantz, 1999). The alterations in the spatial learning tasks were, interestingly, in the direction of fewer errors. This class of compounds also appears to disrupt auditory function in rodents, probably by impairing the development of the cochlea, an effect that appears to be related to the PCBs' action on thyroxine (Crofton and Rice, 1999; Goldey and Crofton, 1998; Rice, 1999). There is some evidence that coplanar PCBs alter performance on tasks that require the acquisition of a response–reinforcer relationship (Rice and Hayward, 1999), as does methylmercury, but this area has not been covered as thoroughly as have discrimination tasks (see Newland and Paletz, 2000).

The non-coplanar PCBs have a very different profile of actions than that seen with the coplanar compounds. Perhaps the most striking effects of exposure to non-coplanar PCBs can be found in procedures that tap memory or discrimination, especially if spatial discriminations are required. Early evidence that PCBs could affect memory came from studies of PCB mixtures in non-human primates (Bowman et al., 1981; Levin et al., 1988; Schantz et al., 1989). Later investigations suggested that these effects might have been due partially to the non-coplanar components of the PCB mixtures. The work of Schantz et al., especially, indicates that non-coplanar PCBs impair performance on delayed spatial discrimination tasks, but that co-planar PCBs and TCDD do not (Schantz, 1996; Schantz et al., 1995,

1997). The effect may be related to disruption of discrimination, rather than memory function, since the impairment of accuracy was not directly related to the delay interval (Levin et al., 1988; Rice and Hayward, 1997).

The different profiles summarized in this section are illustrated in Fig. 2. Methylmercury affects multiple sensory systems and these must be described as related to methylmercury alone because these endpoints, some quite sophisticated, have not been examined with PCBs. Coplanar (non-ortho) PCBs impair audition but probably through a very different mechanism than methylmercury's effects. Both methylmercury and coplanar PCBs affect motor function, transitions under concurrent schedules (response acquisition), and both result in decreased errors on tests of discrimination learning or memory. Neither results in response-bursting under fixed-interval schedules of reinforcement. Non-coplanar (ortho) PCBs diminish performance on memory tasks and spatial discrimination reversals and produce response bursting under fixed-interval schedules of reinforcement.

4. Sensitivity conferred by developmental stage

4.1. Early development

Development is an especially sensitive period for methylmercury, PCB mixtures, and certain PCB congeners. Methylmercury may represent an early, if not the first example of the special sensitivity of the developing nervous system to neurotoxic insult. Maternal exposure to methylmercury has long been associated with long-lasting effects in the offspring in human, primate, and rodent studies (Amin-Zaki and Majeed, 1981; Bakir et al., 1973; Berlin, 1986; Burbacher et al., 1990; Commit-

tee on the Toxicological Effects of Methylmercury, 2000; Newland and Paletz, 2000). Similarly, PCBs seem to be especially neurotoxic when exposure occurs during development in human, primate, and rodent models (Golub and Jacobson, 1995; Schantz, 1996, 1999; Tilson and Kodavanti, 1998). In some studies, exposure ended a year or more before birth and still effects were evident in the offspring (Levin et al., 1988; Schantz et al., 1989).

4.2. Aging

Evidence that the neurotoxicity of methylmercury in humans can be modified by age can be seen in studies of the Minamata cohort (Harada, 1995; Harada et al., 1998). Kinjo has examined a wide range of subjective complaints and 'Activities of Daily Living', a standardized battery used to identify problems associated with aging (Kinjo et al., 1993). Minamata victims reported greater difficulty eating, bathing, face-washing, dressing and using the toilet as well as greater difficulties on sensory, motor, and some cognitive functions than age- and sex-matched controls, with odds ratios ranging as high as 29:1. These declines apparently occurred in the absence of changes in mortality rates of this cohort (Kinjo et al., 1996; Tamashiro et al., 1987).

In studies conducted in Canada, Cree Indians with a history of elevated levels of mercury in their hair (2–31 ppm average levels) were tested on tremor and other motor acts and their results were compared with controls from the Montreal area and with Cree Indians with lower levels of mercury (Beuter et al., 1999a,b; Beuter and Edwards, 1998). The mercury levels were about the same range as those seen in the Iraqi studies of children but the average age of the subjects was 56 years old. Post-hoc analyses compared six subjects with the highest peak exposure, and whose mean age was 10 years older than the larger sample with age-matched controls (Beuter and Edwards, 1998). In these comparisons the effects of mercury appeared larger than in the main cohort, effects that could be due to mercury exposure, age, or an interaction of the two in this preliminary study.

Animal studies confirm age-related deficits in methylmercury and the absence of an increase in mortality. Monkeys exposed to methylmercury during development were impaired in tests of audition and of fine motor control as they aged (Rice, 1996a, 1998). In a study designed explicitly to examine age-related effects of methylmercury, rats were exposed to methylmercury during gestation and lactation, although lactational exposure was minimal (Newland and Reile, 1999). These rats were trained to press a lever at a high rate and to sustain this through 30-min experimental sessions. After the rats were about 1½ years old, and long after methylmercury exposure terminated, the methylmercury

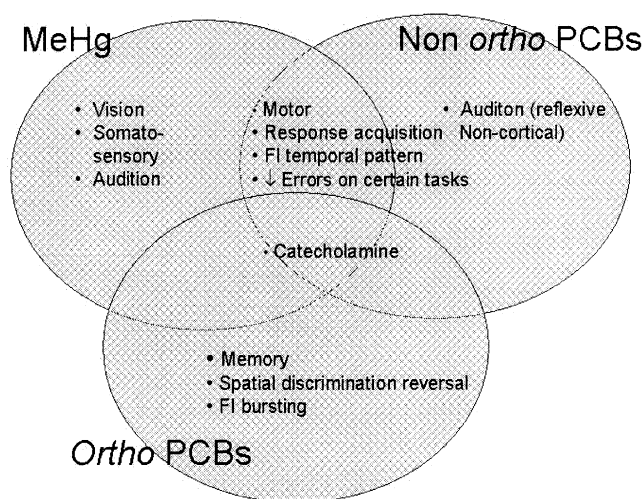


Fig. 2. A Venn diagram summarizing neurobehavioral effects of methylmercury and two classes of PCBs.

exposed rats began to evince difficulty in sustaining this pattern of responding (Newland and Rasmussen, 2000). Reinforcer rate was used to show the ability of the rats to meet the high response rate demanded by the schedule. Fig. 3 shows that the age at which reinforcer rates declined to 50% of individual rats' baselines decreased in a dose-related fashion. All but one control rat completed the experiment with only a minimal rate decline, about 80% of baseline (not visible in the figure but shown in the original paper). Many exposed rats experienced difficulties severe enough that the reinforcer rates declined to zero, at a younger age, and this effect was dose-related. These impairments were represented not by impairments in the entire group, but rather by impairments in specific individuals; some exposed rats resembled controls at the end of the experiment and others showed performance declines. It is not known what the individual differences were that led to deficits in some rats but not others, but such individual differences have been noted with neurotoxicants before (Cory-Slechta et al., 1985).

Effects of early, even prenatal, methylmercury exposure may not become manifest until the organism ages. The exposed rats resembled controls in growth, in survival, and on unchallenged behavior as adults (Newland and Rasmussen, 2000). However, the exposed rats did differ from controls in their sensitivity to certain drugs once challenged. Methylmercury-exposed rats were more sensitive to amphetamine than controls, suggesting that some aspect of monoaminergic neurotransmission was disrupted by developmental exposure (Rasmussen and Newland, 2001).

Ongoing studies of a population of aging (≥ 49 years old) fish-eaters from the Great Lakes suggest cognitive

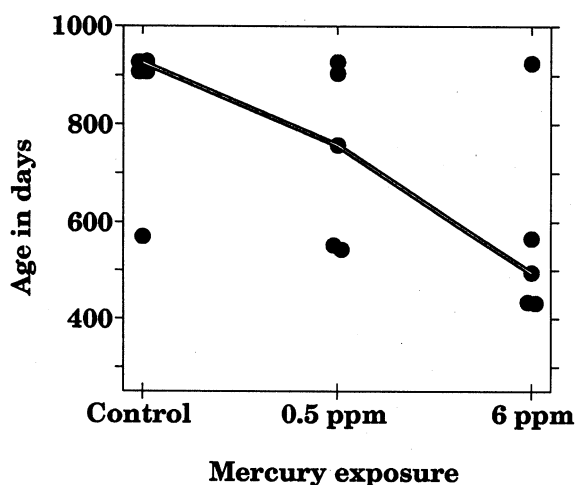


Fig. 3. The age at which the reinforcers earned under a *Differential Reinforcement of High Rate (DRH)* schedule of reinforcement declined to 50% of baseline for at least five consecutive sessions. Under this schedule rats had to press a lever nine times within 4 s to obtain food reinforcement. The line connects the median for each exposure group. From Newland and Rasmussen (2000).

effects of exposure to mixtures of PCBs and dichlorodiphenyl dichloroethene (DDE), containing only trace levels of mercury (Schantz et al., 2001). Exposure to higher levels of PCBs/DDE was associated with impaired performance on tests of memory and cognitive function in this older population exposed adults. Effects may have been restricted to these domains, as effects of PCBs/DDE were not detected on tests of fine motor control (Schantz et al., 1999). While these studies identified effects in an aging population, they do not suggest, yet, an interaction with age. When the subjects were divided into age groups by decades, an interaction with age was not detected, but such an interaction could have been difficult to detect because of a correlation between PCB exposure and age. This study identifies a risk in older adults exposed as adults to PCBs and DDE and indicates that the effects of exposure can be found in similar functional domains, verbal learning and memory, as that seen in younger populations.

The silent damage indicated by the papers reviewed in this section has implications on our ability to detect the effects of neurotoxic insult because such delays raise considerable difficulties in human and animal studies. They also suggest that developmental exposure imposes higher social costs than earlier anticipated because an earlier onset in our inability to care for ourselves means that someone else will have to provide that care, and that comes with a loss of productivity for the ailing individual and a cost to provide the daily care.

5. Sensitivity conferred by toxicant interactions

The primary source of exposure to methylmercury and PCBs is through the diet, and often these toxicants are found in the same foods, and especially fish. This observation is enough to warrant consideration of the possibilities of interactions. Observations that these neurotoxicants interact *in vitro* further supports such considerations.

5.1. PCB/methylmercury interactions

PCBs come in mixtures of coplanar and non-coplanar constituents and each of these components of the mixture can potentially interact with methylmercury that might be present. As noted above and elsewhere (Newland and Paletz, 2000) the effect profiles of methylmercury and coplanar PCBs show some overlap in effects on sensory system, acquisition phenomena, and motor function. The overlap is imperfect and could derive from different neural mechanisms of action. Nevertheless, the overlap is important because of its implications both for health and for assessment. If similarities in effects that are suggested by the animal studies also appear in human populations then exposure

to the two compounds could interact additively. Such overlap also indicates that when evaluating the toxicity of methylmercury and PCBs in populations exposed to both, it is necessary to account for levels of exposure to the different compounds.

Recent *in vitro* work by Bemis and Seegal (1999) suggests that methylmercury and a PCB mixture consisting of Aroclor 1254 and 1260 interact not additively but synergistically. Using striatal punches they examined the effects on dopamine content of different concentrations of methylmercury and the PCB mixture alone and in combination. Both methylmercury and the PCB mixtures produced concentration-related declines in tissue dopamine content and increases in dopamine content in media. The Aroclor mixture was then combined with a methylmercury concentration that, alone, had little or no effect. The increase in media dopamine produced by this combination was several-fold greater than that seen when either the methylmercury or the PCB mixture was applied alone. One contaminant greatly amplified the effects of the other. Levels of one neurotoxicant that, in some cases, were relatively ineffective were far more potent when even small levels of the other toxicant were added. If this finding can be extended to behaving animals or people then it suggests that at least one component found in many diets, could amplify the neurotoxicity of the other.

Interactions between methylmercury and the diet from which the methylmercury is obtained can cloud the picture provided by epidemiology studies. A population under investigation in the Faroe Islands, for example, displays an association between developmental exposure to methylmercury and performance on neuropsychological tests of motor function and verbal abilities (Budtz-Jorgensen et al., 2000; Grandjean et al., 1995, 1997; Weihe et al., 1996). A second population in the Seychelles Islands, also under intense investigation, shows no such association although exposure levels are similar (Crump et al., 2000; Myers and Davidson, 1998; Myers et al., 1995). These populations differ in many ways, but one important difference may be the source of the methylmercury. The Seychellois receive their methylmercury from a diet that is extraordinarily rich in ocean fish, which also contain important nutrients. The Faroe Islanders' methylmercury derives from Pilot Whale, a sea mammal that also contains PCBs. Analyses suggest the presence of methylmercury effects independent of those of PCBs in the Faroe Islanders (Budtz-Jorgensen et al., 1999; Committee on the Toxicological Effects of Methylmercury, 2000; Steuerwald et al., 2000). Nevertheless, the impact of the large differences in the diets is difficult to incorporate satisfactorily. The interactions may be a question that cannot be addressed with epidemiological studies, but rather by the control that is available only in a laboratory. Such laboratory and epidemiology studies

are important to do, not just because they can shed light on methylmercury's neurotoxicity, but also because the rich data base on both methylmercury and PCBs can be used to guide future investigations of mixtures and of extrapolations from the laboratory to the field.

5.2. Summary

Methylmercury and PCBs are neurotoxic. While methylmercury and non-coplanar PCBs have quite different profiles of neurotoxicity, the coplanar PCBs' profile appear to overlap somewhat with methylmercury. This does not necessarily imply a common mechanism of action since behavior reflects the end product of many aspects of nervous system function. It does imply that detecting the effects of mixtures that include methylmercury and PCBs can be difficult at times if their effect profiles overlap and may interact synergistically.

A second form of sensitivity is age. It is well established that the developing organism is especially sensitive to methylmercury. It is becoming evident that the aging organism may be sensitive, too, even if exposure had occurred early in development.

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