Behavioral Effects of Environmental Contaminants

PG 6610

Syllabus

Fall 2001

Course Title: PG 6610 Behavioral Effects of Environmental Contaminants

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Meeting: Monday Wednesday 3:00-4:30 pm
Thach 228 (Psychology Conference Room). Haley Center 3185

Office Hours: Mon, Tuesday 1:00-2:00 or by appointment.

Text: No text. Selected readings

Background. The Toxic Substances Control Act (TSCA), Federal Insecticide, Fungicide, and Rodenticide act (FIFRA), and other pieces of legislation bearing on the health effects of chemicals in the workplace (OSHA), the home (Consumer Product Safety Commission), or the environment (EPA) specifically mention neurobehavioral toxicology as a regulatory concern. The inclusion of nervous system damage in general, and its behavioral manifestations in particular, represents a sea change in public concern over unintended exposure to chemicals. Where cancer has been (and still is) a major concern, the recognition that adverse behavioral effects follow certain types of chemical exposure is increasing.

The heightening public awareness that some toxic substances can act on the nervous system and produce detectable effects presents a major challenge to behavioral neuroscientists. Experimental psychologists and other neuroscientists are being asked to conduct both hazard assessment (are there neurobehavioral effects of some chemical at any dose?) and risk assessment (what is the risk to a population at a specific level of exposure?) for behavioral effects that are not always well understood. The heavy metal, lead, is a prototypical neurotoxicant. Concern over lead poisoning lies not in its carcinogenicity but rather in claims that it lowers scores on IQ tests, retards academic performance, and results in disruptive behavior. The problems posed are daunting: How easy is it to detect a five-point drop in scores on I.Q. tests?

This course will examine toxic substances that primarily on the nervous system. These actions drive the scientific literature aimed at characterization and the identification of mechanisms. They also drive policy decisions regarding release and exposure of these neurotoxicants. The point of departure for this course will be the behavior of the whole, intact organism, but we will depart into several directions. We will examine in some detail how this

behavior is studied and we will examine neuromechanisms, how human and animal behavior can be compared, and how all this bears on policy decisions.

The questions addressed in this course include the following.

- How do we characterize, at the level of behavior, sensory, motor, cognitive, life-span developmental effects of chemicals?
- Can we link effects seen in behavior to neural mechanisms?
- Can we anticipate human neurotoxicity on the basis of studies with nonhuman species and at what level of detail? Will behavior only give us nonspecific toxicity or can mechanistic conclusions? Can we derive precise estimates of adverse, or tolerable, exposure levels for humans based on animal data?
- Can animal studies be conducted economically while still being valid predictors of human effects?
- What populations are most at risk?
- How do laboratory studies get translated into public policy?

Course Structure. The course will cover the basic issues in behavioral toxicology. Principles of behavior will be introduced as required to understand how to assess sensory or motor function, learning and memory, nonspecific behavioral effects, or the reinforcing or irritating properties of chemicals. Principles of toxicology will also be introduced, mostly in the beginning of the course, and these will include the importance of dose-effect relationships, quantitative risk assessment with behavioral endpoints, hazard assessment, routes of exposure, and kinetics. You should leave this course with the skills required to make intelligent decisions about how to assess, read about, or react to events (chemical or otherwise) that have adverse behavioral effects.

There are two ways to structure a course of this type: by chemical or by topic and functional domain. I have chosen a bit of both. First we will cover approaches to evaluating the effects of neurotoxicants in humans and in animal models. We will examine how neurotoxicants affect sensory function, motor function, learning and memory, and development across the lifespan. Having done this we will examine regulatory issues from two perspectives. First, how risk assessment has been conducted with behavior, and recommended improvements in the process. Second, we will examine the larger issue of making policy decisions and communicating hazard and risk to the public. The latter will be covered as we go through some of the representative neurotoxicants.

We will examine three types of neurotoxicants in some detail. Lead is treated first because it more-or-less defined neurobehavioral toxicology and because it represents a success story with many implications. Methylmercury is covered second. Health recommendations about methylmercury are changing, and will continue to change over the next several years, I think. Methylmercury is interesting also because it differs in many ways from lead. Two important differences are that it's "cognitive" effects are minimal, or at least very different from lead's.

Methylmercury also presents an interesting issue regarding the balancing of risks and benefits since it comes packaged in fish, a source of important nutrients.

Solvents are covered last. These produce some acute and some chronic effects so provide an interesting contrast. Also, they are neurotoxicants with abuse potential, making them especially dangerous.

Evaluation will be based upon your score on a take-home test administered in the beginning of the term (1/4 of your grade), class presentations of assigned papers and class participation in general (1/4) and the group project (1/4) and questions submitted to me about the assigned readings (1/4). You will be responsible for presenting papers through the term. These presentations will be about 20 to 40 minutes in length, depending on the nature of the paper you are assigned. *Students not presenting are responsible for reading the paper and must be prepared to discuss it.* We will cover the readings referenced below. For each class I would like for each member to submit a question by e-mail regarding the reading by 9:00 a.m. on the morning of class. I read all of these questions and use them to guide how I handle class. The class memebers form a diverse group and I need to know what is troubling you about the readings. I prefer insightful, general questions, but will give credit for any except the most trivial; we can't all be insightful all the time.

Some Interesting Web Sites

General Site	***Some Subsidiary Sites***	***Web Address.***
U. S. Environmental Protection Agency	General Site	www.epa.gov
	Toxic Release Inventory	http://www.epa.gov/tri/
	Adopt your watershed	www.epa.gov/owowwtr1/watershed/adopt/index.html
Environmental Defense		www.edf.org
Scorecard		www.scorecard.org
Auburn University Environmental Institute		www.auburn.edu /academic/provost/environment/index.html
Agency for Toxic Substances and Disease Registry	Home page	http://www.atsdr.cdc.gov/atsdrhome.html
	HazDat data base	http://www.atsdr.cdc.gov/hazdat.html
Centers for Disease Control	Home Page	www.cdc.gov
	Morbidity and Mortality Weekly Report	www.cdc.gov/epo/mmwr/mmwr.html
Behavioral Toxicology Society		www.behavioraltoxicology.org
Neurobehavioral Teratology Society		nbts.bsbe.umn.edu/
Society of Toxicology		nbts.bsbe.umn.edu/
Duke University Occupational and Environmental Medicine		152.3.65.120/oem/
University of Rochester Environmental Medicine		www.envmed.rochseter.edu

Behavioral Effects of Environmental Contaminants: Class Schedule

Class	Date	Topic	Readings
1	20 Aug	Defining the problem	[1][chapter 1] [2]
2	22 Aug	Biological bases of neurotoxicity	[3]
3	27 Aug	Biological bases of neurotoxicity	[1] [Chapter 2: Biological Bases]
4	29 Aug	Biological markers, dose-effect, kinetics.	[1] [Chapter 3]: Biomarkers) **[4]**
5	5 Sep	Developmental testing: animals.	[5]
6	10 Sep	Human testing: children	[6] [Chapter 3,5] **[7]**
7	12 Sep	Behavior: Elementary principles, acquisition and maintenance and how it can be used.	[8]
8	17 Sep	– Assessing sensory effects. – Chemicals as reinforcing and discriminative stimuli.	
9	19 Sep	– Memory, learning, and other abilities. – Schedule-controlled operant behavior. – Motor effects.	[9]
10	24 Sep	Direct comparisons of human and animal behavior.	[10] **[11]**
11	26 Sep	Pulling it all together: the assessment of risk	[1] [Chapter 6] [12]
12	1 Oct	Lead. Some early history.	**[13]** **[14]**
13	3 Oct	Lead. Effects on children. The Needleman study and its reception.	[15] **[16]**
14	8 Oct	Lead. Replication in human epidemiology studies.	**[17]** **[18]** **[19]**
15	10 Oct	Lead. Animal studies.	[20] [21]
16	15 Oct	Lead. Animal studies.	[22] [23]
17	17 Oct	Lead's lessons.	[24] [25]

Behavioral Effects of Environmental Contaminants: Class Schedule

Class	Date	Topic	Readings
18	22 Oct	Minamata/methylmercury.	[26] [27]
19	24 Oct	Forms of mercury, kinetics, possible mechanisms of action.	[28]
20	29 Oct	Sensorimotor effects of methylmercury. (animal studies).	**[29]** **[30]** [31] **[32]**
21	31 Oct	Methylmercury: Learning, memory, and SCOB.	[33] [34]
22	5 Nov	Methylmercury: – neurochemical interactions – Mercury and aging.	[35] [36] **[37]**
23	7 Nov	– Determining an RfD.	[38] [28]
24	12 Nov	Solvents: Neurochemical mechanisms and stimulus effects (reinforcing and discriminative).	[39] [40]
	14 Nov	Solvents. Sensory effects; memory and learning.	**[41]** **[42]**
25	26 Nov	– Environmental prostheses – Behavioral tolerance	[43] **[44]**
26	28 Nov	Solvents: Behavioral tolerance,	**[45]**
27	3 Dec.	Behavioral Safety	[46] [47] [48]
28	5 Dec	Student projects.	
Finals		Student projects. (final exam period) 10-Dec. 8:00-10:30.	

Classroom Presentations in PG 6610.

Students will present papers from the primary literature. Structure this as a "platform presentation" that might be delivered at a scientific meeting. In your presentation you must describe clearly the reason that the author(s) gave for conducting the research, the methods used, their strengths and weaknesses, the conclusions drawn, and the degree to which these conclusions are supported by the data and the extant literature. The following list contains some of the criteria that I use in grading:

1. Clear description of the research question.
2. Clear description of the methods (with diagrams if that helps).
3. Graphical presentation of the results. You may use the blackboard, transparencies (I will have an overhead projector available) or handouts. We may have power-point available.
4. Presentation of the authors' conclusions, coupled with a critical assessment of the degree to which they are supported. This presentation should be fair to the authors and critical. After all, no single experiment is perfect. Discuss logical inconsistencies, gaps that remain in the literature, the presence (or absence) of information on dose-effect relationships, time-courses of action, and control procedures. Discuss the wider importance (if any) of this paper. To do this you should place the paper into a broader context by drawing from the general readings, lecture, and the literature.

5. For experimental reports, ss a mechanism of action (behavioral or neural) identified, and what is it?

6. What, if any, are the public health implications?

7. What, if any, are the implications for testing or screening strategies?

8. Do the results pertain to hazard identification of risk assessment?

9. Was the experimental design appropriate (experimental reports only)?

    a. Are dose-effect data presented?

    b. Are time course data presented?

    c. Were appropriate controls used?

    d. Are the data pertinent to the behavior of individual subjects?

    e. Were appropriate measures of variability presented, and how to they bear on the conclusions?

Group Projects.

We will leave time for group projects at the end of the term. Depending on the class size, we will have one or two projects, with groups comprising three or four members. Each group can select its topic from the list of suggestions below or can come up with one of its own (subject to the instructor's approval). These groups will be formed after a few weeks of class.

The project will entail providing an evaluation of the risk associated with a putative neurotoxicant. Provide the background for a decision and arrive at a conclusion based upon the data that you present. Evidence should come from the animal laboratory and human epidemiology studies. Be aware of important issues such as dose and mechanisms for neurotoxicity. I would like for the emphasis to be on behavioral work, but that may be supplemented with other studies related to the neurotoxicity of the compound. Each group should describe the population at risk for toxicity (young?, old?), the populations exposed, levels of exposure, and conditions of exposure. You should broaden the question, where appropriate, to describe such issues as the use of the substance and why it is present where it is, the social and political dimensions of risk, whether safety measures can reasonably be applied to limit exposure, why the population exposed is exposed (*i.e.,* is this an environmental justice issue?), wildlife or agricultural animals that might be exposed, or other related areas. This latter list is not meant to be exhaustive, nor is it intended that all those issues be covered. The class is a diverse one so it should be possible to draw from different members to broaden the basis of coverage.

Divide up the chores and present what you have learned at the end of the term. Meet with me before Thanksgiving to tell me what your plans are and so I can know what to expect. Turn in a written report when you give your presentation. Clearly state who did which parts of the report as you will receive a group and individual grade on this. The group's report should be concise and complete (perhaps 30 to 50 pages, plus references)

Suggested topics:

- Methylmercury exposure through fish (you may limit it to Alabama, if you like, or you may feel like taking on the tuna industry).
- Behavioral consequences of exposure to PCB's and dioxins.
- Algal blooms/pfesteria as a potential neurotoxic risk.
- Identify a superfund site or some other site of concern and summarize the neurotoxic potential. (information about chemicals is available on the Web).
- Risk associated with adding manganese to the nation's gasoline supply.
- Hazard and risk associated with pesticide use. You should limit yourself to a type of neurobehavioral effects of pesticides (*e.g.* organophosphates, pyrethroids, carbamates, . . .) and you will need to decide whether to focus on occupation exposure or public health issues. A hot topic now is children's health and pesticide residue. The use of lindane or pyrethroids in the treatment of head lice might be interesting, too.
- Use of teratogens by women of child-bearing age. Pick one (*e.g.,* Vitamin A for acne, anti-seizure compounds for management of epilepsy, ethanol, cocaine, or other abused drugs for recreation.).

Readings

1. National Research Council. (1992). *Environmental neurotoxicology*. Washington, D. C.: National Academy Press.
2. Slovic, P. (1987). Perception of risk. *Science, 236*, 280-285.
3. Kandel, E. R., Schwartz, J. H., & Jessell, T. M. (1995). *Essentials of neural science and behavior*. Stamford, CT: Appleton and Lange.
4. Cox, C., Clarkson, T. W., Marsh, D. O., Amin-Zaki, L., Tikriti, S., & Myers, G. g. (1989). Dose-response analysis of infants prenatally exposed to methyl mercury: An application of a single compartment model to single-strand hair analysis. *Environmental Research, 49*, 318-332.
5. Acuff-Smith, K. D., & Vorhees, C. V. (1999). Neurobehavioral teratology. In R. J. M. Niesink & R. M. A. Jaspers & L. M. W. Kornet & J. M. van Ree & H. A. Tilson (Eds.), *Introduction fo neurobehavioral toxicology: Food and environment*. Boca Raton: CRC Press.
6. Teeter, P. A., & Samrud-Clickerman, M. (1997). *Child neuropsychology: Assessment and intervention for neurodevelopmental disorders*. Boston: Allyn and Bacon.
7. Rohlman, D. S., Gimenes, L. S., Ebbert, C., Anger, W. K., Bailey, S. R., & McCauley, L. (2000). Smiling faces and other rewards: Using the behavioral assessment and research system (bars) with unique populations. *NeuroToxicology, 21*(6), 973-978.
8. Weiss, B., & Cory-Slechta, D. A. (1994). Assessment of behavioral toxicity, *Principles and methods of toxicology* (pp. 1091-1155). New York: Raven Press.
9. Newland, M. C. (1994). Operant behavior and the measurement of motor dysfunction. In B. Weiss & J. L. O'Donoghue (Eds.), *Neurobehavioral toxicity: Analysis and interpretation* (pp. 273-297). New York: Raven Press.
10. Paule, M. G., Forrester, T. M., Maher, M. A., Cranmer, J. M., & Allen, R. R. (1990). Monkey versus human performance in the nctr operant test battery. *Neurotoxicology and Teratology, 12*, 503-507.
11. Paule, M. G., Chelonis, J. J., Buffalo, E. A., Blake, D. J., & Casey, P. H. (1999). Operant test battery performance in children: Correlation with iq. *Neurotoxicology & Teratology, 21*(3), 223-230.
12. Glowa, J. R., & MacPhail, R. C. (1995). Quantitative approaches to risk assessment in neurotoxicology. In L. W. Chang & W. Slikker (Eds.), *Neurotoxicology: Approaches and methods* (pp. 777-787). San Diego: Academic Press.
13. Rosner, D., & Markowitz, G. (1985). A 'gift of god?': The public health controversy over leaded gasoline during the 1920's. *AJPH, 75*, 344-352.
14. Berney, B. (1993). Round and round it goes: The epidemiology of childhood lead poisoning, 1950-1990. *The Milbank Quarterly., 71*, 3-39.
15. Needleman, H. L., Gunnoe, C., Leviton, A., Reed, R., Peresie, H., Maher, C., & Barrett, P. (1979). Deficits in psychologic and classroom performance of children with elevated dentine lead levels. *New England Journal of Medicine, 300*, 689-695.
16. Needleman, H. L. (1992). Salem comes to the national institutes of health: Notes from inside the crucible of scientific integrity. [see comments]. *Pediatrics, 90*(6), 977-981.

17. Bellinger, D., Leviton, A., Waternaux, C., Needleman, H., & Rabinowitz, M. (1989). Low-level lead exposure, social class, and infant development. *Neurotoxicology and Teratology, 10*, 497-503.
18. Bellinger, D., Leviton, A., Waternaux, C., Needleman, H., & Rabinowitz, M. (1987). Longitudinal analyses of prenatal and postnatal lead exposure and early cognitive development. *New England Journal of Medicine, 316*, 1037-1043.
19. Needleman, H. L., Riess, J. A., Tobin, M. J., Biesecker, G. E., & Greenhouse, J. B. (1996). Bone lead levels and delinquent behavior. [see comments]. *JAMA, 275*(5), 363-369.
20. Cory-Slechta, D. A., Weiss, B., & Cox, C. (1985). Performance and exposure indices of rats exposed to low concentrations of lead. *Toxicology and Applied Pharmacology, 78*, 291-295.
21. Cohn, J., & Cory-Slechta, D. A. (1994). Lead exposure potentiates the effects of nmda on repeated learning. *Neurotoxicology and Teratololology, 16*, 455-465.
22. Rice, D. C. (1985). Chronic low-lead exposure from birth produces deficits in discrimination reversal in monkeys. *Toxicology and Applied Pharmacology, 77*, 201-210.
23. Newland, M. C., Yezhou, S., Logdberg, B., & Berlin, M. (1994). Prolonged behavioral effects of in utero exposure to lead or methyl mercury: Reduced sensitivity to changes in reinforcement contingencies during behavioral transitions and in steady state. *Toxicology & Applied Pharmacology, 126*(1), 6-15.
24. Davis, J. M., Elias, R. W., & Grant, L. D. (1993). Current issues in human lead exposure and regulation of lead. *NeuroToxicology, 14*, 15-28.
25. Rice, D. C. (1990). The health effects of environmental lead exposure: Closing pandora's box, *Behavioral measures of neurotoxicity: Report of a symposium* (pp. 243-267). Washington, DC: National Academy Press.
26. Smith, W. E., & Smith, A. M. (1975). *Minamata*. New York: Holt, Rinehart, and Winston.
27. Burbacher, T. M., Rodier, P. M., & Weiss, B. (1990). Methylmercury developmental neurotoxicity: A comparison of effects in humans and animals. *Neurotoxicology and Teratology, 12*, 191-202.
28. Committee on the Toxicological Effects of Methylmercury, N. R. C. (2000). *Toxicological effects of methylmercury*. Washington, DC: National Academy Press.
29. Gunderson, V. M., Grant, K. S., Burbacher, T. M., Fagan, J. F. d., & Mottet, N. K. (1986). The effect of low-level prenatal methylmercury exposure on visual recognition memory in infant crab-eating macaques. *Child Development, 57*(4), 1076-1083.
30. Gunderson, V. M., Grant-Webster, K. S., Burbacher, T. M., & Mottet, N. K. (1988). Visual recognition memory deficits in methylmercury-exposed macaca fascicularis infants. *Neurotoxicology & Teratology, 10*(4), 373-379.
31. Rice, D. C., & Gilbert, S. G. (1990). Effects of developmental exposure to methyl mercury on spatial and temporal visual function in monkeys. *Toxicology & Applied Pharmacology, 102*(1), 151-163.
32. Rice, D. C., & Gilbert, S. G. (1992). Exposure to methyl mercury from birth to adulthood impairs high-frequency hearing in monkeys. *Toxicology & Applied Pharmacology, 115*(1), 6-10.
33. Gilbert, S. G., Burbacher, T. M., & Rice, D. C. (1993). Effects of in utero methylmercury exposure on a spatial delayed alternation task in monkeys. *Toxicology & Applied Pharmacology, 123*(1), 130-136.

34. Rice, D. C. (1998). Lack of effect of methylmercury exposure from birth to adulthood on information processing speed in the monkey. *Neurotoxicology & Teratology, 20*(3), 275-283.

35. Rasmussen, E. B., & Newland, M. C. (2001). Developmental exposure to methylmercury alters behavioral sensitivity to *d* amphetamine and pentobarbital in adult rats. *Neurotoxicology and Teratology, 23*, 45-55.

36. Newland, M. C., & Rasmussen, E. B. (2000). Aging unmasks adverse effects of gestational exposure to methylmercury in rats. *Neurotoxicology & Teratology, 22*(6), 819-828.

37. Kinjo, Y., Higashi, H., Nakano, A., Sakamoto, M., & Sakai, R. (1993). Profile of subjective complaints and activities of daily living among current patients with minamata disease after 3 decades. *Environmental Research, 63*(2), 241-251.

38. Gilbert, S. G., & Grant-Webster, K. S. (1995). Neurobehavioral effects of developmental methylmercury exposure. *Environmental Health Perspectives, 103 (suppl 6)*, 135-142.

39. Wood, R. W. (1979). Reinforcing properties of inhaled substances. *Neurobehavioral Toxicology, 1 Suppl 1*, 67-72.

40. Rees, D. C., Knisely, J. S., Breen, T. J., & Balster, R. L. (1987). Toluene, halothane, 1,1,1-trichloroethane and oxazepam produce ethanol-like discriminative stimulus effects in mice. *Journal of Pharmacology and Experimental Therapeutics, 243*, 931-937.

41. Pryor, G. T., Dickinson, J., Feeney, E., & Rebert, C. S. (1984). Hearing loss in rats first exposed to toluene as weanlings or as young adults. *Neurobehavioral Toxicology & Teratology, 6*(2), 111-119.

42. Pryor, G. T., Howd, R. A., Uyeno, E. T., & Thurber, A. B. (1985). Interactions between toluene and alcohol. *Pharmacology, Biochemistry & Behavior, 23*(3), 401-410.

43. Wood, R. W., Rees, D. C., & Laties, V. G. (1983). Behavioral effects of toluene are modulated by stimulus control. *Toxicology and Applied Pharmacology, 68*, 462-472.

44. Rees, D. C., Wood, R. W., & Laties, V. G. (1989). Evidence of tolerance following repeated exposure to toluene in the rat. *Pharmacology, Biochemistry and Behavior, 32*, 283-291.

45. Bushnell, P. J., & Oshiro, W. M. (2000). Behavioral components of tolerance to repeated inhalation of trichloroethylene (tce) in rats. *Neurotoxicology & Teratology, 22*(2), 221-229.

46. Fox, D. K., Hopkins, B. L., & Anger, W. K. (1987). The long-term effects of a token economy on safety performance in open-pit mining. *Journal of Applied Behavior Analysis, 20*, 215-224.

47. Hopkins, B. L., Conard, R. J., Dangel, R. F., Fitch, H. G., Smith, M. J., & Anger, W. K. (1986). Behavioral technology for reducing occupational exposures to styrene. *Journal of Applied Behavior Analysis, 19*, 3-11.

48. Hopkins, B. L., Conard, R. J., & Smith, M. J. (1986). Effective and reliable behavioral control technology. *American Industrial Hygiene Association Journal, 47*, 785-791.