Applied Occupational and Environmental Hygiene

ISSN: 1047-322X (Print) 1521-0898 (Online) Journal homepage: http://www.tandfonline.com/loi/uaoh20

Exposure Interactions in Occupational/ Environmental Toxicology

B. K. Nelson

To cite this article: B. K. Nelson (1997) Exposure Interactions in Occupational/Environmental Toxicology, Applied Occupational and Environmental Hygiene, 12:5, 356-361, DOI: 10.1080/1047322X.1997.10389518

To link to this article: http://dx.doi.org/10.1080/1047322X.1997.10389518

Published online: 25 Feb 2011.

Exposure Interactions in Occupational/Environmental Toxicology

B.K. Nelson

Division of Biomedical and Behavioral Science, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health C-24, 4676 Columbia Parkway, Cincinnati, Ohio 45226

This article highlights the importance of evaluating the whole person when health professionals diagnose potential toxicity from occupational and/or environmental exposure. Health professionals must consider interactions of combined exposures to toxic agents resulting from the personal lifestyle of an individual, along with various drugs which the person may be taking. In addition, health professionals must evaluate potential family or home exposures from use of chemicals in the home, as well as from chemicals that may enter the home by way of workplace-contaminated clothing or other items brought home from work. Toxic exposures to chemical and physical agents and other modifying factors (e.g., diurnal variations due to shift work or stress) to which individuals may be exposed occupationally or environmentally must also be considered. Readers are reminded that many modifying factors may impinge on occupational and environmental toxicity. NELSON, B.K.: EXPOSURE INTERACTIONS IN OCCUPATIONAL/ENVIRONMENTAL TOXICOLOGY. APPL. OCCUP. ENVIRON. HYG. 12(5):356–361; 1997. PUBLISHED 1997 BY AIH.

Interactions of various workplace and environmental chemicals and physical conditions, ingestion of alcohol, and other factors have produced unexpected, and often undesirable, effects. For example, "degreasers' flush" has been described in people exposed to trichloroethylene at work who would stop to have a beer on the way home from work.[1] Some individuals developed unsightly red blotches on their faces. During one of Stewart's experimental studies of breath decay curves of trichloroethylene, he noted one subject who developed the blotches. Upon closer scrutiny, this individual was found to have violated the experimental protocol and consumed beer—thus prompting a study to investigate degreasers' flush.[1] Similar effects were seen in workers exposed to dimethylformamide who consumed beer.[2] A third example of exposure to an environmental agent may also have involved alcohol in a man who developed dermatitis after he took up golf.[3] The condition persisted over the summer months but waned during the winter months. Upon investigation, the physicians who treated this man found that Thiram® was used as a fungicide on the golf course. It was later shown that ethanol consumption exacerbates the effects of Thiram, but whether or not the case subject's effects were altered by ethanol consumption is not clear.

These examples highlight the potential for interactions in occupational and environmental medicine. Attesting to the worldwide interest in combined exposures/chemical mixtures are a number of recent workshops and symposia, as well as regulatory discussions.[4–11] This article is not intended to review all of the published reports of interactions in occupational or environmental exposures, as several review-type papers or books are available for general toxicology,[12,13] carcinogenesis,[14–16] developmental toxicology,[17,18] experimental human neurobehavioral toxicology,[19,20] and statistical approaches and risk calculations.[21–27] Rather, the purpose of this article is to stimulate health professionals' thinking concerning the wide variety of factors that may impinge on exposed individuals to affect their health. Instead of focusing on a few trees in the forest, readers are encouraged to view the forest—to evaluate the whole-person exposures rather than isolated toxic agents. Although combined agent interactions have not been studied as much in occupational/environmental medicine as in clinical medicine, drug interactions are frequently encountered in clinical medicine.[28,29] Hence, this article cites a few examples of interactions of a drug with other factors which affect the drug's efficacy or toxicity. In these cases the cited example is a drug, but a similar effect could be seen with a chemical exposure. Just as patients may self-administer various kinds of drugs (e.g., over-the-counter drugs or other prescription drugs) and interactive effects can be undesirable,[30] individuals may encounter various exposures with unexpected and undesirable effects.

Interactions may be antagonistic, additive, or synergistic, although prediction of the type of interactive effect is impossible.[17,18,31–34] Furthermore, different types of interactions may be seen at various points along the dose–effect curves, including biphasic or other responses.[33,35] For example, a certain threshold of either agent may be necessary before an interaction would occur (e.g., caffeine is not a strong developmental toxicant, but may exert strong interactive effects in developmental toxicology.[17,36,37] The order of, and time interval between, administration of the two agents can markedly affect the type and extent of interaction seen.[33] Qualitatively, interactions can be either pharmacokinetic (altering the absorption, biotransformation, distribution, or disposition of chemicals) or pharmacodynamic (altering the association of agents with receptors).[30,32,38]

Interactions should not be confused with issues of allergy or sensitive populations, in which an individual's response to a toxic agent is extraordinary.[39] Various factors affect an individual's reaction to a toxic agent, including idiosyncratic reactions (abnormal response due to the genetic makeup of the individual), age factors, unexpected reactions due to the sex of the individual, size (unusually small or large individuals), and general health status (e.g., a compromised immune system).

Although putative adverse interactions among several drugs

 1047-322X/97/1205-356$0.00/6 Published 1997 by AIH · PII S1047-322X(96)00421-9

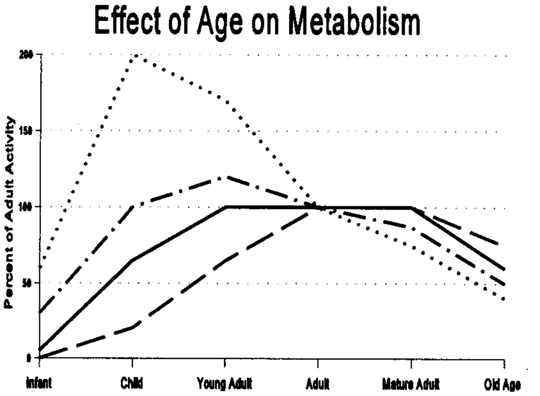

FIGURE 1. Effects of age on metabolism (hypothetical curves). Some drugs or chemicals are metabolized at a higher rate in children than adults. Others are metabolized more poorly in children than adults. Most drugs and chemicals are probably metabolized more poorly in aged individuals than in middle-aged individuals.

are commonly recognized, the likelihood of unexpected toxicity due to concurrent exposures to occupational and environmental hazards may be less understood. The effect of occupational/environmental exposures of individuals can be adversely influenced by personal lifestyle (e.g., general health conditions, age, drug-taking behavior, exposures through hobbies, etc.), along with family and home influences (e.g., diet, secondhand smoke, other exposures in the home) and modifying factors in the occupational or more general environment (e.g., temperature, shift work, stress). Interactions among all of these influences must be considered when evaluating health problems in occupational and environmental settings.

Personal/Lifestyle Influences

Various personal and lifestyle influences, such as general health conditions (e.g., coexisting diseases, immune status, obesity), age, sex, and drug-taking behavior (prescription and social) can all affect the toxicity of an occupational exposure.[40] For example, the age of exposed individuals affects the toxicity of some drugs and chemicals.[41–44] Figure 1 presents hypothetical curves representing various chemicals that have metabolic profiles similar, or very different, at several ages. As illustrated, some enzymes may reach adult levels very early in life; others may take longer to achieve those levels. Some enzymes may peak much higher in children and then drop off to adult levels. Whatever the developmental profile, the alterations in metabolism in aging individuals are becoming more and more of a concern with the aging of the human population.[41,45,46] There are several examples of drugs and chemicals known to be metabolized differently in adults and children. For example, acetaminophen is less toxic to children than it is to adults.[47] In contrast, children are more susceptible to the effects of lead.[48] Young experimental animals are more susceptible to the toxicity of *n*-propyl alcohol[49] and vinyl chloride[50] than are adults. The evidence from vinyl chloride is exemplary: Exposure of newborn Sprague–Dawley rats to 6000 or 10,000 ppm vinyl chloride for 4 hours per day for 5 days, with the rats then held for 2 years, induced a high incidence of liver angiosarcoma and hepatocellular carcinoma; in contrast, almost no carcinogenic effect was observed in 11-week-old rats exposed under the same regimen to vinyl chloride.[51] Even personal habits such as hand-washing have been documented to affect contamination with toxic agents.[52]

Drugs that alter chemical toxicity are also well recognized, and may affect biomarkers of occupational/environmental exposure.[40] For example, ethyl alcohol interacts with various industrial chemicals.[53–58] Caffeine alters the developmental toxicity of numerous drugs and chemicals,[17,36,37] even interacting to produce teratogenicity in a strain of mice which is ordinarily resistant to acetazolamide teratogenicity.[59] The markedly increased incidence of tumors in those who smoke and are exposed to asbestos is well known.[60] Interactions of smoking (or chewing) tobacco with lead exposure were noted early in this century.[61] Disulfiram enhances the toxicity of ethylene dibromide.[62–64]

Family/Home Influences

Various factors in the family and home environment may influence the toxicity of occupational exposures, including diet, second-hand smoke, other contaminants in the home (such as paints and varnishes), and stress. For example, both the composition of the diet and the relative timing of meals can increase, delay, or decrease the rate of absorption of various drugs and chemicals from the stomach.[65] The levels of certain nutrients can exacerbate the toxicity of oxygen radicals, as well as other chemicals.[66]

The National Institute for Occupational Safety and Health has recently summarized numerous cases of family or home contamination by chemicals inadvertently brought home from the workplace.[67] Other contaminants may be present in the home because of the environment in which the home is located. For example, perchloroethylene may be found in homes or apartments located near dry-cleaning establishments, with concentrations even exceeding those permitted in the workplace![68–70] Blood lead levels may be higher in children living in industrialized areas than in those living in more rural environments.[71]

Occupational/Environmental Influences

Chemical–Chemical Interactions

Repeated exposure to the same (or a structurally similar chemical) can affect the toxicity of certain chemicals, probably through the induction or repression of metabolizing enzymes. The ability of various ketones to enhance the toxicity of one another is well known.[33,72] Ketones can interact with some pesticides[16,73] (e.g., the LD_{50} of carbon tetrachloride in rats pretreated with 10 ppm dietary clordecone decreased from 2.8 ml/kg to only 0.042 ml/kg[74]) and halogenated hydrocarbons.[75–78] Various alcohols can potentiate the toxicity of some ketones.[79,80] (Interestingly, in the homologous series of eight alcohols investigated, about one half increased only the hepatotoxicity of the ketones, while the other half increased hepatotoxicity as well as lethality.[79] Many cases of cancer are thought to result from interactions of several chemicals.[14]

Chemical–Physical Agent Interactions

Perhaps less well known than chemical–chemical interactions are concurrent exposures to chemical and physical agents.

Physical agents such as noise, heat, and vibration can affect chemical hazards. For example, interactive effects of simultaneous occupational exposure to solvents and noise on hearing have been reported.(81) This subject will be discussed more completely below.

In addition to the common physical hazards of fluctuating temperatures, vibration, and noise, there is another physical agent that can be found in nearly every work setting: nonionizing electromagnetic radiation. One type of nonionizing radiation, radiofrequency (RF) radiation (3 kHz to 300 MHz), is used in a number of industries, including communications, electronics, medicine, and manufacturing. Moreover, many workers in these industries, such as those working with microelectronics, plastic sealers, and electrosurgical units, are exposed to RF radiation in conjunction with the chemicals they use. For many years the risks of exposure to RF radiation were presumed to be small because RF radiation has insufficient energy to ionize molecules or atoms (as opposed to its higher-energy counterpart, ionizing radiation). Even exposure to RF radiation levels high enough to heat body tissue was thought to result in only short-term health effects, although developmental toxicity has recently been described for hyperthermic levels of RF radiation.(82–85)

Previous animal research has also indicated that hypothermia or hyperthermia induced by changes in environmental temperature can increase the toxic effects of some chemicals and drugs.(86,87) Therefore, a study was conducted to determine if RF radiation would increase the adverse developmental outcomes of the industrial solvent, 2-methoxyethanol (2ME). This glycol ether is found in various industries (especially in some degreasing solvents and in paints and varnishes). It produces developmental toxicity in every species of experimental animals tested to date (including nonhuman primates), and possibly in humans.(88) The incidence of congenital malformations was studied in rats that were exposed to RF radiation alone, 2ME alone, and the two combined on gestation day 13.(89) RF radiation caused malformations in 30 percent of the rat fetuses, and 2ME produced malformations in 14 percent of the fetuses. Yet, combined exposure to RF radiation and 2ME induced external malformations in 76 percent of the fetuses. In addition to the synergism observed in the incidence of malformations (see Figure 2), the malformations were more severe in the combined exposure group than in either single-agent exposure group. Subsequent studies using several doses of 2ME and RF radiation confirmed these findings.(90–93)

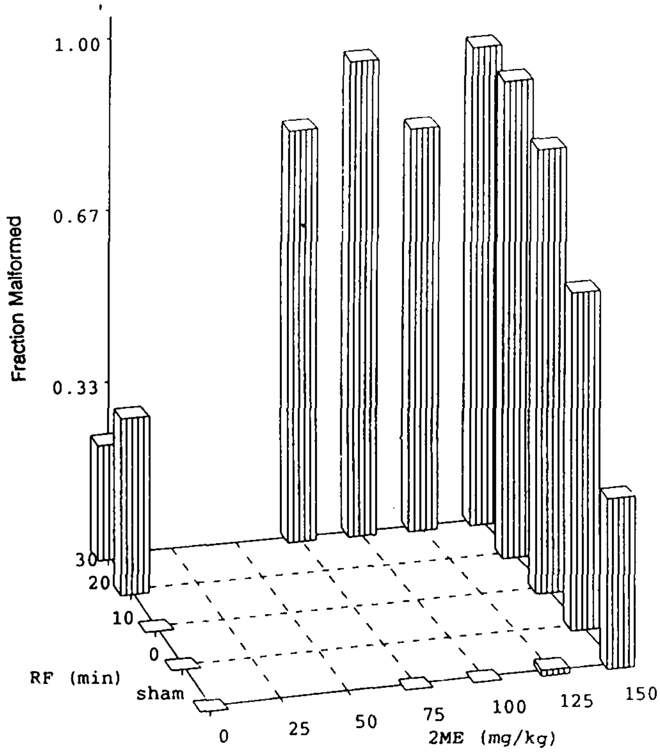

FIGURE 2. Example of a graph illustrating the interactive effects of 2ME and RF radiation in rats.(89) The graph depicts the percentage of fetuses with forepaw malformations after exposure on gestation day 13.

Chemical–Environmental Interactions

Environmental conditions such as circadian cycles, seasonal changes, temperature, humidity, noise, and stress can all affect chemical toxicity. For example, the toxicity of certain chemicals, as well as the therapeutic efficacy of some drugs, is affected by the time of day and season of year of administration.(94–97) Obviously, such circadian patterns have clear implications for shift workers.(98,99)

The effect of environmental temperature on the toxicity of methylmercury in rats is presented in Figure 3 (data from Yamaguchi *et al.*(100)). Young male Wistar JCL rats were acclimated to room temperature (22°C) for 15 days. Groups of 23 control and 23 experimental rats were then placed in rooms maintained at 11°, 22°, or 33°C (60 ± 5 percent relative humidity). Experimental rats in each group were injected subcutaneously with 5 mg/kg methylmercury every third day for up to 60 days. Every 15 days, five randomly selected control and experimental rats were sacrificed and blood, kidney, and brain samples were collected for determination of

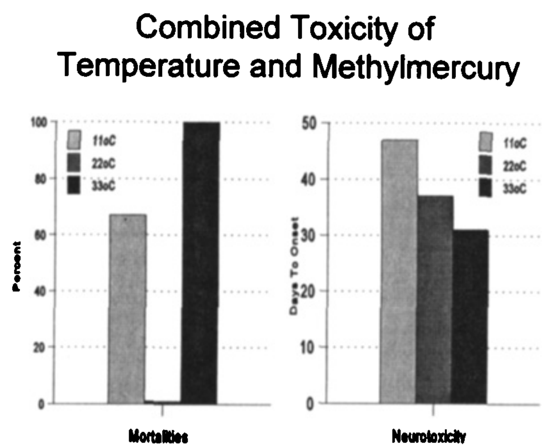

FIGURE 3. Graph illustrating the toxicity of combined hypothermia and hyperthermia on methylmercury toxicity in rats.(100) The left panel reveals the highest mortalities under hyperthermic conditions, intermediate mortalities under hypothermic conditions, and no mortalities at room temperature. The right panel shows the most rapid onset of neurotoxicity under hyperthermic conditions and the slowest onset under hypothermic conditions.

total mercury and methylmercury. Regular observations were made for hind leg crossing as a measure of neurotoxicity, and for mortalities. Generally, the hyperthermic exposed group had higher levels of total mercury and methylmercury, exhibited the most rapid onset of neurotoxicity, and had the highest toxicity (all died by day 45). The hypothermic exposed rats had lower brain levels, similar blood levels, and higher kidney levels of both total mercury and methylmercury. The onset of neurotoxicity was slower than in controls, but there were more mortalities than in controls.[100]

Several studies suggest that combined exposure to noise and solvents enhances hearing loss in humans.[101–103] For example, investigators conducted interviews and hearing tests on approximately 200 workers in the printing and paint manufacturing industries. The subjects included 50 control workers, 50 workers exposed to noise, 39 workers exposed to organic solvents, and 51 workers exposed to noise and toluene. The investigators concluded that concurrent occupational exposure to excessive levels of toluene and noise increased the probability of developing a hearing loss. The effect of combined exposure also suggested a synergistic interaction between noise and toluene on hearing loss, with the level of hearing loss much greater in the workers exposed to both hazards than would be expected by adding the effects of each agent.[81]

The effects of inhaled methanol on pituitary and testicular hormones of rats were found to depend on whether or not the rats were acclimated to the chambers prior to exposure.[104] The authors suggested that the rats acclimated to the exposure chambers were less stressed than those not acclimated to the chambers. Restraint stress (30 minutes) increased mortalities induced by cocaine in mice from 17 to 58 percent.[105]

Summary

As described in this article, various kinds of interactions must be evaluated by occupational/environmental health professionals as they diagnose potential toxicity. Health professionals must consider the total person, including interactions of toxic agents with personal lifestyles of the individuals, along with various drugs which the person may be taking. They must also evaluate potential family or home exposures, as well as toxic exposures to chemical and physical agents and other modifying factors to which people may be exposed occupationally or environmentally. Many diseases may well be the result of complex interactions among a wide variety of exposures and modifying conditions.

References

1. Stewart, R.D.; Hake, K.L.; Peterson, J.E.: "Degreasers' Flush." Arch. Environ. Health 29:1–5 (1974).
2. Lyle, W.H.: Alcohol Interaction with a Workplace Chemical (Case History). Occup. Health 31:265–267 (1979).
3. Shelley, W.B.: Golf-Course Dermatitis Due to Thiram Fungicide. JAMA 188:415–417 (1964).
4. Environmental Protection Agency: Guidelines for the Health Risk Assessment of Chemical Mixtures. Fed. Reg. 51(185): 34014–34025 (1986).
5. Environmental Protection Agency: Risk Assessment Guidelines of 1986. EPA 600-8-87/045. U.S. Government Printing Office, Washington, DC (1987).
6. National Research Council: Complex Mixtures—Methods for In Vivo Toxicity Testing. National Academy Press, Washington, DC (1988).
7. Mumtaz, M.M.; Sipes, I.G.; Clewell, H.J.; Yang, R.S.H.: Symposium Overview: Risk Assessment of Chemical Mixtures: Biologic and Toxicologic Issues. Fund. Appl. Toxicol. 21:258–268 (1993).
8. Environmental Protection Agency: Chemical Mixtures and Quantitative Risk Assessment. Toxicology 105:109–442 (1995).
9. European Conference on Combination Toxicology: Food Chem. Toxicol (1997, In press).
10. National Occupational Research Agenda: Mixed Exposures. National Institute for Occupational Safety and Health, Cincinnati, OH (1996).
11. Manninen, O.: International Society for Complex Environmental Studies: Seventh International Conference on the Combined Effects of Environmental Factors. Arch. Complex Environ. Stud. (1997, In press).
12. Goldstein, R.S.; Hewitt, W.R.; Hook, J.B. (Eds.): Toxic Interactions. Academic Press, New York (1990).
13. Mauderly, J.L.: Toxicological Approaches to Complex Mixtures. Environ. Health Persp. 101(Suppl. 4):155–165 (1993).
14. Reif, A.E.: Synergism in Carcinogenesis. J. Natl. Cancer Inst. 73:25–39 (1984).
15. Schmael, D.; V.C.H. Publishers, Inc. (Ed.): Combination Effects in Chemical Carcinogenesis. Weinheim, Germany (1988).
16. Mehendale, H.M.: Impact of Chemical Interactions on the Development of Cancer. In: Carcinogenicity and Pesticides: Principles, Issues, and Relationships, pp. 122–141. N.N. Ragsdale and R.E. Menzer, Eds. American Chemical Society, Washington, DC (1989).
17. Nelson, B.K.: Interactions in Developmental Toxicology: A Literature Review and Terminology Proposal. Teratology 49: 33–71 (1994).
18. Kavlock, R.J.; Perreault, S.D.: Multiple Chemical Exposure and Risks of Adverse Reproductive Function and Outcome. In: Toxicology of Chemical Mixtures: Case Studies, Mechanisms, and Novel Approaches, Ed. by R. Yang, Academic Press, NY, pp. 245–297 (1994).
19. Dick, R.D.: Acute Exposure Research with Organic Solvents: The NIOSH Experience. Appl. Psychol. Int. Rev. 41:219–228 (1992).
20. Dick, R.D.: Neurobehavioral Assessment of Occupationally Relevant Solvents and Chemicals in Humans. In: Handbook of Neurotoxicology, pp. 217–322. L.W. Chang and R.S. Dyer, Eds. Marcel Dekker, New York (1995).
21. Seiler, F.A.; Scott, B.R.: Mixtures of Toxic Agents and Attributable Risk Calculations. Risk Anal. 7:81–90 (1987).
22. Künstler, K.; Klein, R.G.: Mathematical Approaches in Combination Effects. In: Comb. Eff. Chem. Carcinogen, pp. 31–43. D. Schmaehl, V.C.H. Publishers, Inc., (Ed.). Weinheim, Germany (1988).
23. Chou, T.-C.; Rideout, D.C. (Eds.): Synergism and Antagonism in Chemotherapy. Academic Press, New York (1991).
24. Vaughn, E.: Individual and Cultural Differences in Adaptation to Environmental Risks. Am. Psychol. 48:673–680 (1993).
25. Narotsky, M.G.; Weller, E.A.; Chinchilli, V.M.; Kavlock, R.J.: Nonadditive Developmental Toxicity in Mixtures of Trichloroethlene, Di(2-ethylhexyl)phthalate, and Heptachlor in a 5×5×5 Design. Fund. Appl. Toxicol. 27:203–216 (1995).
26. Mumtaz, M.M.; DeRosa, C.T.; Durkin, P.R.: Approaches and Challenges in Risk Assessment of Chemical Mixtures. In: Toxicology of Chemical Mixtures, pp. 565–597 (1995).
27. Seed, J.; Brown, R.P.; Olin, S.S.; Foran, J.A.: Chemical Mixtures: Current Risk Assessment Methodologies and Future Directions. Regul. Toxicol. Pharmacol. 22:76–94 (1995).
28. Rideout, D.C.; Chou, T.-C.: Synergism, Antagonism, and Potentiation in Chemotherapy: An Overview. In: Synergism and Antagonism in Chemotherapy, pp. 3–60. T.-C. Chou and D.C. Rideout, Eds. Academic Press, New York (1991).

29. Fu, K.F.: Interactions of Chemotherapeutic Agents and Radiation. Front. Radiat. Ther. Oncol. 26:16–30 (1992).
30. Nies, A.S.: Principles of Therapeutics. In: Goodman and Gilman's The Pharmacological Basis of Therapeutics, 8th ed., pp. 16–30. A.G. Gilman, T.W. Rall, A.S. Nies, and P. Taylor, Eds. Pergamon Press, New York (1990).
31. Berenbaum, M.C.: What Is Synergy? Pharmacol. Rev. 41:93–141 (1989).
32. Klaassen, C.D.: Principles of Toxicology. In: Goodman and Gilman's The Pharmacological Basis of Therapeutics, 8th ed., pp. 49–61. A.G. Gilman, T.W. Rall, A.S. Nies, and P. Taylor, Eds. Pergamon Press, New York (1990).
33. Plaa, G.L.; Vezina, M.: Factors to Consider in the Design and Evaluation of Chemical Interaction Studies in Laboratory Animals. In: Toxic Interactions, pp. 3–30. R.S. Goldstein, W.R. Hewitt, and J.B. Hook, Eds. Academic Press, New York (1990).
34. Klaassen, C.D.; Eaton, C.D.: Principles of Toxicology. In: Casarett and Doull's Toxicology: The Basic Science of Poisons, 4th ed., pp. 12–49. M.O. Amdur, J. Doull, and C.D. Klaassen, Eds. Pergamon Press, New York (1991).
35. MacDonald, J.R.; Gandolfi, A.J.; Sipes, I.G.: Acetone Potentiation of 1,1,2-Trichloroethane Hepatotoxicity. Toxicol. Lett. 13:57–69 (1982).
36. Ritter, E.J.; Scott, Jr., W.J.; Wilson, J.G.; et al.: Potentiative Interactions Between Caffeine and Various Teratogenic Agents. Teratology 25:95–100 (1982).
37. Ritter, E.J.; Scott, Jr., W.J.; Randall, J.L.; Ritter, J.M.: Teratogenicity of Di(2-ethylhexyl) Phthalate, 2-Ethylhexanol, 2-Ethylhexanoic Acid, and Valproic Acid, and Potentiation by Caffeine. Teratology 35:41–46 (1987).
38. Skalko, R.G.; Kwasigroch, T.E.: The Interaction of Chemicals During Pregnancy: An Update. Biol. Res. Preg. Perinatol. 4:26–35 (1983).
39. Calabrese, E.J.: Pollutants and High-Risk Groups–The Biological Basis of Increased Human Susceptibility to Environmental and Occupational Pollutants. Wiley Interscience, New York (1978).
40. Alessio, L.; Apostoli, P.; Crippa, M.: Influence of Individual Factors and Personal Habits on the Levels of Biological Indicators of Exposure. Toxicol. Lett. 77:93–103 (1995).
41. Guzelian, P.S.; Henry, C.J.; Olin, S.S. (Eds.): Similarities and Differences between Children and Adults: Implications for Risk Assessment. ILSI Press, Washington, DC (1992).
42. Woodhouse, K.; Wynne, H.A.: Age-related Changes in Hepatic Function–Implications for Drug Therapy. Drugs & Aging 2:243–255 (1992).
43. Meydani, M.: Impact of Aging on Detoxification Mechanisms. In: Nutritional Toxicology, pp. 49–66. F.N. Kotsonis, M. Mackey, and J. Hjelle, Eds. Raven Press, New York (1994).
44. Thomas, J.A.; Tschanz, C.: Nutrient-Drug Interactions. In: Nutritional Toxicology, pp. 139–148. F.N. Kotsonis, M. Mackey, and J. Hjelle, Eds. Raven Press, New York (1994).
45. Ilmarinen, J. (Ed.): The Aging Worker. Scand. J. Work Environ. Health 17(Suppl 1):1–141 (1991).
46. Hurrell, J.J.; Lindstrom, K.: Comparison of Job Demands, Control and Psychosomatic Complaints at Different Career Stages of Managers in Finland and the United States. Scand. J. Work Environ. Health 18(Suppl. 2):11–13 (1992).
47. Kauffman, R.E.: Acute Acetaminophen Overdose: An Example of Reduced Toxicity Related to Developmental Differences in Drug Metabolism. In: Similarities and Differences Between Children and Adults: Implications for Risk Assessment, pp. 97–103. P.S. Guzelian, C.J. Henry, and S.S. Olin, Eds. International Life Sciences Institute Press, Washington, DC (1992).
48. Davis, J.M.; Grant, L.D.: The Sensitivity of Children to Lead. In: Similarities and Differences Between Children and Adults: Implications for Risk Assessment, pp. 150–162. P.S. Guzelian, C.J. Henry, and S.S. Olin, Eds. International Life Sciences Institute Press, Washington, DC (1992).
49. Nelson, B.K.; Brightwell, W.S.; MacKenzie-Taylor, D.R.; et al.: Teratogenicity of n-Propanol and Isopropanol Administered at High Inhalation Concentrations to Rats. Fd. Chem. Toxicol. 26:247–254 (1988).
50. Swenberg, J.A.; Fedtke, N.; Fishbein, L.: Age-related Differences in DNA Adduct Formation and Carcinogenesis of Vinyl Chloride in Rats. In: Similarities and Differences Between Children and Adults: Implications for Risk Assessment, pp. 163–171. P.S. Guzelian, C.J. Henry, and S.S. Olin, Eds. International Life Sciences Institute Press, Washington, DC (1992).
51. Maltoni, C.; Lefemine, C.; Cilberti, A.; et al. Experimental Research on Vinyl Chloride Carcinogenesis. In: Archives of Research on Industrial Carcinogenesis. C. Maltoni and M.A. Mehlman, Eds. Princeton Scientific, Princeton, NJ (1984).
52. Sherlock, J.C.; Barltrop, D.; Evans, W.H.; et al.: Blood Lead Concentrations and Lead Intake in Children of Different Ethnic Origin. Human Toxicology 4:513–519 (1985).
53. Cornish, H.H.; Adefuin, J.: Ethanol Potentiation of Halogenated Aliphatic Solvent Toxicity. Am. Ind. Hyg. Assoc. J. 27:57–61 (1966).
54. Savolainen, H.; Helojoki, M.; Tengen-Junnila, M.: Behavioral and Glial Cell Effects of Inhalation Exposure to Styrene Vapour with Special Reference to Interaction of Simultaneous Peroral Ethanol Intake. Acta Pharmacol. Toxicol. 46:51–56 (1980).
55. Strubelt, O.: Interactions Between Ethanol and Other Hepatotoxic Agents. Biochem. Pharmacol. 29:1445–1449 (1980).
56. Snyder, C.A.; Baarson, K.A.; Goldstein, B.D.; et al.: Ingestion of Ethanol Increases the Hematotoxicity of Inhaled Benzene in C57BL Mice. Bull. Environ. Contam. Toxicol. 27:175–180 (1981).
57. Woolverton, W.L.; Balster, R.L.: Behavioral and Lethal Effects of Combinations of Oral Ethanol and Inhaled 1,1,1-Trichloroethane in Mice. Toxicol. Appl. Pharmacol. 59:1–7 (1981).
58. Hills, B.W.; Venable, H.L.: The Interaction of Ethyl Alcohol and Industrial Chemicals. Am. J. Ind. Med. 3:321–333 (1982).
59. Beck, S.L.; Urbano, C.M.: Acetazolamide with Caffeine Causes Exencephaly in "Resistant" SWV Mice. Reproductive Toxicology 7:123–129 (1993).
60. Steenland, K.; Thun, M.: Interaction Between Tobacco Smoking and Occupational Exposures in the Causation of Lung Cancer. J. Occup. Med. 28:110–118 (1986).
61. Oliver, T.: Lead Poisoning: From the Industrial, Medical, and Social Points of View. Paul B. Hoeber, New York (1914).
62. National Institute for Occupational Safety and Health: NIOSH Current Intelligence Bulletin No. 23: Ethylene Dibromide and Disulfiram Toxic Interaction. DHEW (NIOSH) Pub. No. 78: 145. NIOSH, Cincinnati, OH (1978).
63. Plotnick, H.B.: Carcinogenesis in Rats of Combined Ethylene Dibromide and Disulfiram (Letter to the Editor). J. Am. Med. Assoc. 239:1609 (1978).
64. Plotnick, H.B.; Weigel, W.W.; Richards, D.E.; et al.: The Effect of Dietary Disulfiram Upon the Tissue Distribution and Excretion of ^{14}C-1,2-Dibromoethane in the Rat. Res. Commun. Chem. Pathol. Pharmacol. 26:535–545 (1979).
65. Thomas, J.A.; Tschanz, C.: Nutrient-Drug Interactions. In: Nutritional Toxicology, pp. 139–148. F.N. Kotsonis, M. Mackey, and J.J. Iijelle, Eds. Raven Press, New York (1994).
66. Parke, D.V.; Ioannides, C.: The Effects of Nutrition on Chemical Toxicity. Drug Metabolism Reviews 26:739–765 (1994).
67. National Institute for Occupational Safety and Health: Report to Congress on Workers' Home Contamination Study Conducted Under the Worker's Family Protection Act (29 U.S.C. 671a). NIOSH, Cincinnati, OH (1995).

68. Schreiber, J.S.; House, S.; Prohonic, E.; et al.: An Investigation of Indoor Air Contamination in Residences Above Dry Cleaners. Risk Analysis 13:335–344 (1993).
69. Aggazzotti, A.; Fantuzzi, G.; Predieri, G.; et al.: Indoor Exposure to Perchloroethylene (PCE) in Individuals Living with Dry-Cleaning Workers. The Science of the Total Environment 156:133–127 (1994).
70. Aggazzotti, A.; Fantuzzi, G.; Righi, E.; et al.: Occupational and Environmental Exposure to Perchloroethylene (PCE) in Dry Cleaners and Their Family Members. Arch. Environ. Health 49:487–493 (1994).
71. Hofstetter, I.; Ewers, U.; Freier, I.; et al.: Study of Lead and Cadmium Contamination in Stolberg Children. Oeffentliches Gesundhistswesen 52:232–237 (1990).
72. Plaa, G.L.; Hewitt, W.R.; duSouich, P.; et al.: Isopropanol and Acetone Potentiation of Carbon Tetrachloride-Induced Hepatotoxicity: Single Versus Repetitive Pretreatments in Rats. J. Toxicol. Environ. Health 9:235–250 (1982).
73. Rao, S.B.; Mehendale, H.M.: Protection from Chlordecone (Kepone®)-Potentiated CCl_4 Hepatotoxicity in Rats by Fructose 1,6-Diphosphate. Int. J. Biochem. 21:949–954 (1989).
74. Klingensmith, J.S.; Mehendale, H.M.: Potentiation of CCl_4 Lethality by Clordecone. Toxicol. Lett. 11:149–154 (1982).
75. Hewitt, W.R.; Brown, E.M.; Cote, M.G.; et al.: Alteration of Chloroform-Induced Nephrotoxicity by Exogenous Ketones. In: Nephrotoxic Mechanisms of Drugs and Environmental Toxins, pp. 357–365. G. Porter, Ed. Plenum Publishing Corp., New York (1982).
76. Hewitt, W.R.; Brown, E.M.; Plaa, G.L.: Relationship Between Carbon Skeleton Length of Ketonic Solvents and Potentiation of chloroform-Induced Hepatotoxicity in Rats. Toxicol. Letters 16:297–304 (1983).
77. Mehendale, J.M.; Klingensmith, J.S.: *In Vivo* Metabolism of CCl_4 by Rats Pretreated with Chlordecone, Mirex, or Phenobarbital. Toxicol. Appl. Pharmacol. 93:247–256 (1988).
78. Raisbeck, M.F.; Brown, E.M.; Kanchanapangka, S.; Hewitt, W.R.: Ketonic Potentiation of Haloalkane-Induced Nephrotoxicity. In: Toxic Interactions, pp. 321–367. R.S. Goldstein, W.R. Hewitt, and J.B. Hook, Eds. Academic Press, New York (1990).
79. Ray, S.D.; Mehendale, H.M.: Potentiation of CCl_4 and $CHCl_3$ Hepatotoxicity and Lethality by Various Alcohols. Fund. Appl. Toxicol. 15:429–440 (1990).
80. Juntunen, J.: Alcoholism in Occupational Neurology: Diagnostic Difficulties with Special Reference to the Neurological Syndromes Caused by Exposure to Organic Solvents. Occup. Neurol. (Acta Neurol. Scandinav. Suppl. 92) 66:89–108 (1982).
81. Morata, T.C.; Dunn, D.E.; Kretschmer, L.W.; et al.: Effects of Occupational Exposure to Organic Solvents and Noise on Hearing. Scand. J. Work Environ. Health 19:245–254 (1993).
82. Lary, J.M.; Conover, D.L.: Teratogenic Effects of Radiofrequency Radiation. IEEE Engineer. Med. Biol. Mag. March: 42–46 (1987).
83. Lary, J.M.; Conover, D.L.; Foley, E.D.; et al.: Teratogenic Effects of 27.12 MHz Radiofrequency Radiation in Rats. Teratology 26(3):299–309 (1982).
84. Lary, J.M.; Conover, D.L.; Johnson, P.H.; et al.: Teratogenicity of 27.12 MHz Radiation in Rats Is Related to Duration of Hyperthermic Exposure. Bioelectromagnetics 4:249–255 (1983).
85. Lary, J.M.; Conover, D.L.; Johnson, P.H.; et al.: Dose-Response Relationship Between Body Temperature and Birth Defects in Radiofrequency-Irradiated Rats. Bioelectromagnetics 7:141–149 (1986).
86. Keplinger, M.L.; Lanier, G.E.; Deichmann, W.B.: Effects of Environmental Temperature on the Acute Toxicity of a Number of Compounds in Rats. Toxicol. Appl. Pharmacol. 1:156–161 (1959).
87. Weihe, W.H.: The Effect of Temperature on the Action of Drugs. Ann. Rev. Pharmacol. 13:409–425 (1973).
88. National Institute for Occupational Safety and Health: Criteria for a Recommended Standard: Occupational Exposure to Ethylene Glycol Monomethyl Ether, Ethylene Glycol Monoethyl Ether, and Their Acetates. DHHS (NIOSH) Pub. No. 91-119. NIOSH, Cincinnati, OH (1991).
89. Nelson, B.K.; Conover, D.L.; Brightwell, W.S.; et al.: Marked Increase in the Teratogenicity of the Combined Administration of the Industrial Solvent 2-Methoxyethanol and Radiofrequency Radiation in Rats. Teratology 43(6):621–634 (1991).
90. Nelson, B.K.; Conover, D.L.; Shaw, P.B.; et al.: Interactive Developmental Toxicity of Radiofrequency Radiation and 2-Methoxyethanol in Rats. Teratology 50:275–293 (1994).
91. Nelson, B.K.; Conover, D.L.: Experimental Interactions of Glycol Ethers with Chemical and Physical Agents: Developmental Toxicology. *Occup. Hyg.* 2(1–6):303–310 (1996).
92. Nelson, B.K.; Conover, D.L.; Shaw, P.B.; et al.: Interactive Effects of Radiofrequency Radiation on the Developmental Toxicity of 2-Methoxyethanol in Rats. *J. Appl. Toxicol.* 17:31–39 (1997).
93. Nelson, B.K.; Conover, D.L.; Krieg, E.F.; et al.: Interactions of Radiofrequency Radiation-Induced Hyperthermia and 2-Methoxyethanol Teratogenicity in Rats. *Bioelectromagnetics* 18, In press (1997).
94. Haus, E.: Pharmacological and Toxicological Correlates of Circadian Synchronization and Desynchronization. In: Shift Work and Health, a Symposium. P.G. Rentos and R.D. Shepard, Eds. DHEW Publ. No. (NIOSH) 76-203:87–117. NIOSH, Cincinnati, OH (1976).
95. Reinberg, A.; Smolensky, M.H.: Circadian Changes of Drug Disposition in Man. Clin. Pharmacokinetics 7:401–420 (1982).
96. Smolensky, M.H.; Paustenback, D.J.; Scheving, L.E.: Biological Rhythms, Shiftwork, and Occupational Health. In: Patty's Industrial Hygiene & Toxicology, 2nd ed., Vol. 3B: Biological Responses, pp. 175–312. L. Cralley and L. Cralley, Eds. John Wiley & Sons, New York (1985).
97. Belanger, P.M.: Chronopharmacology in Drug Research and Therapy. Advances in Drug Research 24:1–80 (1993).
98. Rentos, P.G.; Shepard, R.D. (Eds.): Shift Work and Health . . . A Symposium. HEW Pub. No. (NIOSH) 76-203. National Institute for Occupational Safety and Health, Cincinnati, OH (1976).
99. Novak, R.D.; Smolensky, M.H.: Biological Rhythms, Shiftwork, and Occupational Health. In: Patty's Industrial Hygiene & Toxicology, 3rd ed., Vol. 3B, pp. 319–438. L.J. Cralley, L.V. Cralley, and J.S. Bus, Eds. John Wiley & Sons, New York (1995).
100. Yamaguchi, S.; Shimojo, N.; Sano, K.; et al.: Effects of Environmental Temperatures on the Toxicity of Methylmercury in Rats. Bull. Environ. Contam. Toxicol. 32:543–549 (1984).
101. Johnson, A.-C.; Juntunen, L.; Nylén, P.; et al.: Effect of Interaction Between Noise and Toluene on Auditory Function in the Rat. Acta Otolaryng. (Stockh.). 109:34–40 (1988).
102. Morata, T.C.; Nylén, P.; Johnson, A.-C.; Dunn, D.E.: Auditory and Vestibular Functions After Single or Combined Exposure to Toluene: A Review. Arch. Toxicol. 69:431–443 (1995).
103. Franks, J.R.; Morata, T.C.: Ototoxic Effects of Chemicals Alone or in Concert with Noise: A Review of Human Studies. In: Scientific Basis of Noise-Induced hearing Loss, pp. 437–446. A. Axelsson, H. Borchgrevink, R.P. Havernik, et al., Eds. Thieme Medical Pub., New York (1996).
104. Cooper, R.L.; Mole, M.L.; Rehnberg, G.L.; et al.: Effect of Inhaled Methanol in Pituitary and Testicular Hormones in Chamber Acclimated and Non-acclimated Rats. Toxicology 71:69–81 (1992).
105. Pudiak, C.M.; Bozarth, M.A.: Cocaine Fatalities Increased by Restraint Stress. Life Sci. 55:379–382 (1994).