Project Clean Environment for Healthy Kids

Recognition and Management of Health Problems Related to Pesticide Exposure Acute & Chronic Effects

by Marion Moses, MD

For further information contact:

Virginia Ruiz
Project Coordinator
Farmworker Justice Fund, Inc.
1010 Vermont Ave., NW, Suite 915
Washington, D.C. 20005
(ph) 202-783-2628
(fax) 202-783-2561
email: vruiz@nclr.org

Dr. Marion Moses
Pesticide Education Center
P.O. Box 225279
San Francisco, CA 94142-5279
(ph) 415- 665-4722
(fax) 415-665-2693
email: pec@igc.org
www.pesticides.org

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Acute and Chronic Health Effects of Pesticide Exposures

by Marion Moses M.D.
Pesticide Education Center

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Chapter 1

Introduction and Overview

Pesticides are toxic chemicals deliberately released into our environment to kill or harm living things. They can also kill or harm human beings. Pesticides are ubiquitous global contaminants of air, water, rain, snow, fog, soil, land and aquatic ecosystems, even the Arctic ice pack. Pesticide residues contaminate body fluids and tissues of living creatures all over the world, including newborn babies.

History:
Pests were considered as biblical type plagues[a] until the French began using lime sulfur to control downy mildew on grapes in 1854. Chemical pest control began in the U.S. in 1867 with the use of Paris Green (copper-acetoarsenite) for control of the Colorado potato beetle. The discovery of Bordeaux mix (hydrated lime and copper sulfate) in 1880 led to the manufacture of metal based compounds for use in agriculture[1]. Aircraft were first used to spray crops in Europe in 1922, and in the U.S. in 1926[b].

Some Landmarks in Pest Control

1854	Use of lime sulfur as a fungicide on grapes in France
1867	Use of Paris Green against the Colorado potato beetle in the U.S.
1880	Discovery of Bordeaux mixture.
1926	First use of aircraft to apply pesticides in the U.S.[b]
1939	Discovery of insecticidal properties of DDT
1940s	Marketing of DDT, parathion, 2,4-D, and 2,4,5-T.
1947	Passage of FIFRA (Federal Insecticide, Fungicide, and Rodenticide Act).
1962	Publication of Rachel Carson's Silent Spring
1970	Creation of theEnvironmental Protection Agency.
1972	Authority for administration of FIFRA passed from USDA to the EPA.
1975	Passage of major amendments to FIFRA
1996	Passage of the Food Quality Protection Act amendments to FIFRA.

In 1939, the Swiss chemist Paul Muller discovered the insecticidal properties of DDT, for which he received the 1948 Nobel prize. The success of DDT in averting typhus outbreaks during World War II made it the first war in history in which more soldiers died of their wounds than of disease[2]. German scientists experimenting with nerve-gas during World War II synthesized the first organophosphate insecticide, parathion, marketed in 1943. The Dow Chemical Company introduced the phenoxy herbicides 2,4-D and 2,4,5-T (constituents of Agent Orange) in the 1940s. DDT came onto the U.S. market in 1945 after the war embargo was lifted

Farmers saw insects and weeds that had been plagues for known human history, succumb to these miracle chemicals. DDT was promoted as "a boon to all mankind" (1946 advertisement in "Time" magazine). The World Health Organization was so impressed with DDT's effect on the anopheles mosquito, it even thought (incorrectly) that the insecticide would eliminate malaria by 1955. Chemicals dominated university research in entomology and agronomy for decades. Agricultural chemical companies were the main source of funds for the research and support of graduate students.

Resistance and Secondary Outbreaks: Two major problems were soon apparent – resistance and secondary outbreaks. Not all pests were killed by the potent biocides. A very small number of survivors passed their resistance on to future generations. Larger amounts of increasingly toxic combinations of pesticides were needed to combat resistance. Over time many pests could not be controlled at all, beginning the search for the next generation of chemicals.

The other major problem was the broad spectrum of pesticide activity. They not only killed the "bad" insects, but also their natural predators, the "good" ones. Insects that had been kept under control by natural predators for centuries became major pests themselves, resulting in severe secondary outbreaks requiring even more pesticides to control. The more pesticides were used, the more were needed, and use skyrocketed. This led to what a biocontrol expert called "the pesticide treadmill"[3].

Effects on Non-target Species: The new biocides caused many occupational, accidental, animal and wildlife poisonings and deaths, and widespread contamination of food, water, and the ecosystem. Concerns about potential human health and ecosystem impacts were countered by warnings from the agricultural chemical industry, farm interests, and Departments of Agriculture that mass starvation and untold deaths from disease would result if practices were changed. Agricultural production values dominated the debate in legislatures throughout the world. The toxic agricultural infrastructure, and the unecological monoculture that both fed and resulted from it, continued to expand.

[a] The Spanish word for pesticide – plaguicida – reflects this.
[b] Delta Airlines started as a company spraying arsenate insecticides on cotton for boll weevil control in the southern U.S..

Silent Spring: In 1962, Rachel Carson's book *Silent Spring*[4] dramatically changed the way the world thought about pesticides. A wildlife biologist, Carson described the devastating ecological effects of DDT and related pesticides she called "elixirs of death". She raised public awareness of the interdependence of all life-systems and concerns about potential human health effects. She was the birth mother of the environmental movement. Fallout from the book jolted legislators out of their torpor, and provided grist to the environmentalist mill that grinds to this day.

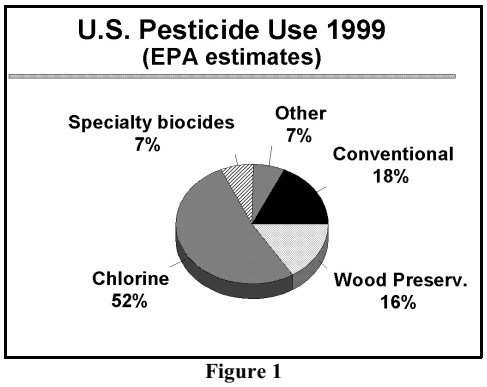


Figure 1

Pesticide Regulation: In the 1970s, the first attempts to fix the more egregious deficiencies in pesticide law began. In 1972, authority for the regulation of pesticide production and use passed from the U.S. Department of Agriculture to the U.S. Environmental Protection Agency (EPA) formed in 1970.

In 1975, major amendments to FIFRA (the Federal Insecticide Fungicide and Rodenticide Act) required reevaluation by 1985 of all registered products then on the market. Studies of potential chronic effects, including cancer, birth defects, neurological damage, and genetic damage in laboratory animals became requirements for registration of pesticides.

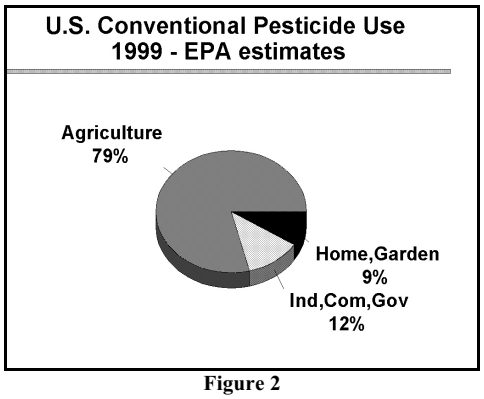


Figure 2

Hundreds of thousands of products remained on the market in scientific limbo, during a lengthy and often litigious process. The 1985 deadline was continually extended by Congress, and some pesticides registered before 1984 have still not yet been evaluated for chronic health effects.

In 1996, the Food Quality Protection Act (FQPA) amendments to FIFRA and the Federal Food, Drug and Cosmetic Act (FFDCA) began another major reevaluation process. FQPA requires a reassessment of all food tolerances (the maximum amount of pesticide residues allowed on food), by replacing FIFRA's cost-benefit analysis with a "reasonable certainty of no harm" standard. The EPA was required to take three additional steps to determine whether a pesticide met this new health-based standard: (1).Take into account aggregate exposure from food, water, and home and garden uses; (2). Add an additional ten-fold margin of safety (or higher if necessary), to protect infants and children; (3). Consider cumulative risks from all pesticides which have a common mechanism of activity; for example, organophosphates insecticides, which have the same basic mechanism of toxicity and biological activity[5].

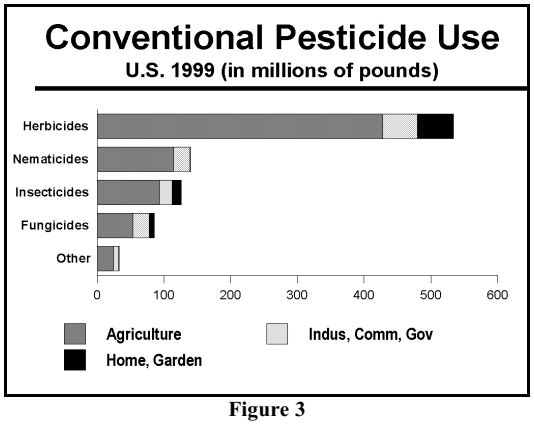


Figure 3

To date 4,000 of the 9,721 tolerances requiring reassessment have been completed[6].

Pesticide Registration:
All pesticides products must be registered with the EPA before they can be sold and used. All pesticides are registered in one of two categories–general use, or restricted use. Restricted use pesticides can only be applied by a certified pesticide applicator or one working under the direct supervision of a certified applicator[c]. The same pesticide active ingredient can be registered as a general or restricted use product depending on it concentration, formulation, and use.

EPA registers pesticides only for a particular use; this information must be stated on the label. Any use of a pesticide for a non-registered or non-label purpose is illegal. A pesticide registered for use on apples cannot be used on pears unless it is also registered for that use. A pesticide registered to control cockroaches cannot be used for termites unless it is also registered for that use.

[c] Code of Federal Regulations (Chapter 40, Part 152.160-175) .

All products have a unique EPA registration number on the label, and a product without one is not legal for sale or use. “Chinese Chalk” and ”Tres Pasitos” are examples of illegal products. Pest control products which are not chemical pesticides do not require an EPA number, including Roach Motels®, rat and mouse traps, sticky fly paper, some herbs and plant oils, among other products

Registered Products*:* In 1939 there were 32 pesticide products registered in the U.S., primarily inorganic compounds containing arsenic, copper, lead, mercury, nicotine, pyrethrums, and sulfur. In 2000, there were about 900 active ingredient pesticides and 1,200 inert ingredients registered with the EPA. The number of similar products on the market containing these active ingredient pesticides is not reported by the EPA which allows registration of the “brand name” products under different “house labels”. Estimates are that 100,000 to 400,000 registered products are on the market, with many being duplicates of the same product formulated by different companies.

California estimates there were 920 active ingredient pesticides formulated into 12,038 pesticides products registered in the State in 2000[7]. The number of active ingredients drops to 542 if multiple forms of the same pesticide, and mixtures of the pesticide with other ingredients are excluded from the count. For example, there are eight different 2,4-D esters and amines, any one of which can be found in 604 registered products.

Production Companies:
Naturally occurring compounds are used as pesticides, but most are synthetic compounds made from petrochemicals. The EPA estimates that 118 basic producers (18 major) produced an average of 1.6 billion pounds of pesticides in the U.S. in 1998 and 1999. Major U.S. manufacturers include Dow, Dupont, Monsanto, and FMC. The U.S. imported an average of 300 million pounds of pesticides in 1998 and 1999[8]. European manufacturers whose products are widely sold in the U.S. include Bayer, Cheminova, and Syngenta.

Both U.S. and foreign basic producers sell the technical product to other companies which mix and package them under their own labels and brand names. In the U.S. there are 150 to 200 national formulators, 2,000 local formulators, 250 to 350 national distributors, and 16,900 other pesticide distributors and establishments.

Pesticide Applicators*:* The EPA estimates there are 803,423 private certified applicators in the U.S.; most of them are farmers. There are 33,100 commercial pest control companies, and 384,092 certified commercial applicators (exterminators, pest control operators). The total number of pesticide applicators on farms and in pest control companies is not known, but is many times greater than the number certified. This is because FIFRA allows applicators who are not certified to work “under the supervision” of a certified applicator. It is not uncommon for one person on a farm or in a company to be certified and several others to work under their supervision. The “supervisor” need not be present, as long as they are reachable by telephone or other means.

Signal Words on the Label

Danger	*Peligro*	Highly Toxic
Warning	*Aviso*	Moderately Toxic
Caution	*Precaución*	Least Toxic

Pesticide Labeling:
Active ingredients: The law requires the name of all active ingredients to be on the pesticide label in decreasing order of their percentage in the product. Pesticides have both a common and a chemical name. The chemical name is often the only name on the list in products sold over-the-counter. Trade name products with similar names can have different ingredients, especially over-the-counter products.

Table 1
Types of Inert Ingredients

Adhesives	Emulsifiers
Adjuvants	Feeding stimulants
Abscission agents	Harvest aids
Anti-foam/defoamers	Penetrants
Anti-transpirants	Solvents
Carriers	Spreaders
Compatibility agents	Stickers
Deposition agents	Surfactants
Dispersants	Suspension/gelling agents
Drift control agents	Water absorbants
Dyes/brighteners	Water softeners
Encapsulation agents	Wetting agents

Inert ingredients:
Pesticide products contain other chemicals besides pesticides called “inert” or “other” ingredients. They are added to enhance effectiveness by dissolving the pesticide, to keep it from settling out, to make it stick better to surfaces it is applied to, to make it last longer, and for other purpose (see Table 1). They are called inert because they are not active as pesticides, but this does not mean they are not toxic, or biologically active. In 1987 the EPA categorized all inert ingredients into four lists.

List 1: Inerts of toxicological concern. This could be based on carcinogenicity, adverse reproductive effects, neurotoxicity or other chronic effects, birth defects, adverse ecological effects or the potential for bioaccumulation (see Appendix D).

List 2: Potentially toxic inerts/high priority for testing. They could be structurally similar to chemicals known

to be toxic, or have data suggesting a basis for concern (see Appendix D).

List 3: Inerts of unknown toxicity, which did not have data supporting their inclusion on any of the other lists. There are 1,500 ingredients on this list.

List 4: Minimal hazard or risk inerts, generally regarded as innocuous. In 1989 List 4 was further refined into

List 4A: Inerts generally regarded as safe, and

List 4B: Inerts for which EPA has sufficient information to reasonably conclude that the current use pattern in pesticide products will not adversely affect public health or the environment (see Appendix D).

Only the names or List 1 inert ingredients are required to be on label. For lists 2 to 4, only the percentage in the product is required . Some products have a statement on the label that it contains petroleum distillates, xylene grade aromatic solvents, or other toxic inert ingredients.

Signal words: All pesticides must have a signal word on the label - Danger, Warning, or Caution. Some labels include the Spanish equivalent – Peligro, Aviso, Precaucion. These signal words refer to the immediate hazard of the product – its potential to cause acute poisoning. It does not refer to chronic toxicity or potential long-term effects. See Chapter 2 for the relationship of signal words to EPA Toxicity Categories I to IV. The signal word can be anywhere on the label and is sometimes very hard to find; it is usually on the front. A skull and crossbones on the label means a small amount of the pesticide can be fatal to humans.

Table 1

Agricultural Pesticide Use - U.S. 1999[7]
(in millions of pounds)

Atrazine	Her	74-80	Chloropicrin	Fum	8-10
Glyphosate	Her	67-73	Copper hydroxide	Fun	8-10
Metam-sodium	Fum	60-64	Chlorpyrifos	Ins	8-10
Acetochlor	Her	30-35	Alachlor	Her	7-10
Methyl bromide	Fum	28-33	Propanil	Her	7-10
2,4-D	Her	28-33	EPTC	Her	7-9
Malathion	Ins	28-32	Dimethenamid	Her	6-8
Metolachlor	Her	26-30	Mancozeb	Fun	6-8
Trifluralin	Her	18-23	Dicamba	Her	6-8
Pendimethalin	Her	17-22	Terbuphos	Ins	5-7
Dichloropropene	Fum	17-20	Ethephon	PGR	5-6
Metolachlor-s	Her	16-19	Cyanazine	Her	4-8
Chlorothalonil	Fun	9-11			

Proposition 65 Warning: California has a consumer disclosure law passed in 1986 that requires a warning statement on retail products that contain chemicals known to cause cancer or birth defects. Most home use pesticide products are exempt from this requirement. A pesticide that does carry the Proposition 65 warning is paradichloro-benzene, the active ingredient in moth balls, which is also found in air fresheners and other consumer products not marketed as pesticides.

Pesticide Registration Groups:

EPA registers pesticides in five different groups (see Figure 1):

1. Conventional pesticides - 18%. This category includes include herbicides, insecticides, fungicides, nematicides, rodenticides, mollucicides, avicides, and pisicides. EPA estimates 912 million pounds were used in 1999, most in agriculture (see Figure 2).

2. Wood preservatives - 16%. This category includes creosote, pentachlorophenol, and chromated copper arsenate (CCA). Most of the 820 million pounds used annually is coal tar creosote on railroad cross ties, utility poles, and pilings for docks and foundations.

3. Chlorine and hypochlorites - 52%. This category includes 2.6 billions pounds used for water treatment–1.57 billion pound for disinfection of potable and waster water, and one billion pounds for disinfection of recreational water.

Proposition 65 Warning

Notice: California has determined that a chemical contained in this product causes cancer based on tests performed on laboratory animals.

(From a moth bar containing 99.35% paradichloro-benzene, and a closet freshener containing 99.5%).

4. Speciality biocides - 7%. This category includes 343 million pounds of which 230 million is used for recreational and water treatment (excluding chlorine and hypochlorites). Sixty-two million pounds are disinfectants and sanitizers used for industrial/institutional applications and household cleaning products. Fifty one million pounds are biocides used in

Table 2

Pesticides for Which One Million Pounds or More Used California 2000[10]
(in millions of pounds)

Sulfur	62.90	Petroleum distillates	2.31
Petroleum oil.	19.75	Chlorpyrifos	2.10
Metam-sodium	12.84	Cryolite	1.96
Methyl bromide	10.86	Calcium hydroxide	1.90
Glyphosate	4.64	Propanil	1.36
1.3-dichloropropene	4.44	Diuron	1.34
Copper sulfate	4.18	Propargite	1.33
Mineral oil	3.90	Maneb	1.20
Chloropicrin	3.79	Trifluralin	1.16
Copper hydroxide	3.31	Diazinon	1.05
Sodium clorate	2.52	Molinate	1.03
Sulfuryl fluoride	2.42	Thiobencarb	1.01

adhesives and sealants, leather, synthetic latex polymers, metalworking fluids, paints and coatings, petroleum products, plastics, and mineral slurries.

5. Other pesticides -7%. This category includes 219 million pounds of sulfur and petroleum oils, and 113 million pounds used in insect repellents, moth control products, as well as other miscellaneous chemicals for nonpesticidal purposes.

Agricultural Use:
Agriculture is the largest user of conventional pesticides in the U.S. (see Figure 2). The USDA (U.S. Department of Agriculture estimates agricultural pesticide spending at $7.6 billion in 1999, which represents 4% of total production expenditures[9].

Table 1 shows the top 15 pesticides used in agriculture in the U.S. in 1999 based on EPA estimates. The primary use of the top pesticide, atrazine, is as a herbicide on corn. Table 2 shows the pesticides for which one million pounds or more were used in California in 2000, based on pesticide use reports which are required by state law. Total use in the California was 1.88 billion pounds in 2000 and 1.54 billion pounds in 2001. Agriculture accounts for 82% of use in California. Table 3 shows petroleum oil used as pesticides or in pesticide produces in the state.

California Use: California has its own pesticide registration system and is the only state that mandates full reporting of all farm and commercial pesticide use. Prior to 1990 only restricted use pesticides were required to be reported, but since then all use must be reported. See Table 2 and Table 3 for high volume pesticides used in the State in 2000[10].

Table 3

Oil Pesticides - California 2000[10]
(in millions of pounds)

	1993	2001
Kerosene	153,411	48,295
Mineral oil	2,709,864	3,603,445
Petroleum distillates	3,200,539	1,741,593
Petroleum distillates, aromatic	81,286	2,472
Petroleum distillates, refined	21,107	842,733
Petroleum hydrocarbons	834,097	498,760
Petroleum oil, paraffin based	446,829	342,100
Petroleum oil, unclassified	21,756,717	15,414,858

Home and Garden Use
EPA estimates that 74% of the 77 million households in the U.S. used a pesticide product in 1999. Insecticides and disinfectants were used by 56%, repellents by 50%, herbicides by 39%, and fungicides by 14%. Table 4 shows the most commonly used pesticide active ingredients based on EPA estimates from proprietary data. They include both commercial and consumer use. There are no data that categorize over-the-counter -sales directly to consumers.

Table 4

Home, Garden Pesticide Use U.S. 1999[7]
(in millions of pounds)

Paradichlorobenzene*	Fum	30-35
2,4-D	Her	7-9
Deet	Rep	5-7
Glyphosate	Her	5-7
MCPP	Her	3-5
Dicamba	Her	3-5
Chlorpyrifos	Ins	2-4
Carbaryl	Ins	2-4
Diazinon	Ins	2-4
Naphtlelene	Fum	2-4
Benefin	Her	1-3
Malathion	Ins	1-3
DCPA	Her	1-3

* Ingredient in mothballs, also used in air fresheners and other consumer products.

Table 5 shows non-agricultural and commercial pesticide use in California in 2000. The state does not report use data on pesticides sold directly to consumers. Three of the chemicals in Table 5 are termiticides–sulfuryl fluoride (Vikane), liquid nitrogen, and methyl bromide. Chlorpyrifos (Dursban) is also widely used in termite control, but disaggregated data on this specific use are not reported. Two of the most widely used home insecticides, chlorpyrifos (Dursban) and diazinon are now banned for sale over-the-counter, but agricultural and commercial use continues.

A survey found that 85% of homes treated for insect in Los Angles, 61% of homes in Seattle, and 69% of Iowa homes used lawn and garden weed treatments[11]. A survey of 308 Minnesota households with children aged 3-13 found that 97% had pesticides in the home and 88% used them. There were 850 unique products with an average of 6 stored and 3 used per household. The most common active ingredients found were Deet, piperonyl butoxide, pyrethrins, MCPA, and chlorpyrifos[12].

Table 5
Non-agricultural Pesticide Use
California 2000

Sulfuryl fluoride	Fum*	2,406,133
Glyphosate	Her	1,104,001
Diuron	Her	654,640
Diazinon	Ins	519,120
Chlorpyrifos	Ins	428,918
Copper sulfate	Her	394,986
Liquid nitrogen	Ins*	391,479
Methyl bromide	Fum*	275,793
Permethrin	Ins	240,988
Cypermethrin	Ins	126,098

* For termite control.

In a survey of household family pesticide use of 238 Missouri families with children 10 years of age or younger, 45 had children with brain cancer, 108 children with other cancers, and 85 healthy children. Ninety-eight percent of the families used pesticides at least once per year, and 64% more than five times per year. Eighty-one percent of the families used pesticides during pregnancy and 70% during the first 6 months of life of their children. Fifty-seven percent applied pesticides to their yards, and 20% used yard herbicide services. Spray can or spray liquids were used by 50% of the families, dusts, bombs, and no-pest strips by 15%; pet collars by 50.4%, pet shampoos by 40%, and dusts for ticks and fleas by 20% [13].

Lawns: If the American lawn was a single crop, it would be the largest in the U.S, covering some 50 thousand square miles–roughly the size of Pennsylvania. A recent article described the American lawn as "...a stunningly elaborate enabler of petrochemical addition", for which the annual expenditure is 30 billion dollars a year [14]. A large percentage of the herbicides shown in Tables 4 and 5 are used on lawns.

Table 6
Industry, Commercial, Government Use U.S. 1999[7]
(in millions of pounds)

2,4-D	Her	17-20
Glyphosate	Her	11-14
Copper sulfate	Fun	5-7
Chlorpyrifos	Ins	3-5
MSMA	Her	2-4
Chlorothalonil	Fun	2-4
Diruon	Her	2-4
Malathion	Ins	1-3
Trichlopyr	Her	1-3

Industry, Commercial, Government Use:
Table 6 shows EPA estimates for industrial, commercial, and government use. The largest use is herbicides for treatment of rights-of-way including highways, power lines, and railroads. Drug Enforcement Administration use of herbicides in heroin, cocaine, and marijuana producing crops are included in this category.

Banned and Severely Restricted Pesticides
See Appendix E for a list of pesticides that are banned or for which use is severely restricted in the U.S.

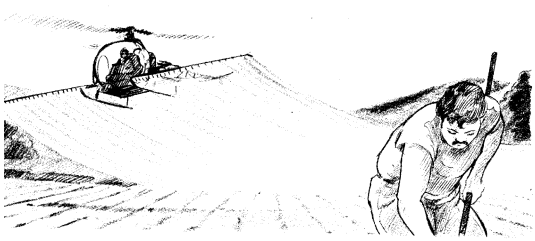
References:

1. Ordish G. 1968. 150 years of crop pest control. World Rev Pest Control 7(4):204-213.
2. Zinsser H. *Rats, Lice, and History*. Bantam Books 1935, reissued 1971.
3. VanDenBosch R. *The Pesticide Treadmill*. University of California Press. Berkeley, California. 1977.
4. Carson R. *Silent Spring*. Houghton Mifflin, Boston, Massachusetts. 1962.
5. USGAO. 2000. Children and Pesticides. New Approach to Considering Risk is Partly in Place. GAO/HEHS-00-175. Gov. Printing Office. Washington D.C.
6. USEPA. 2002. Office of Pesticide Programs FY 2001 Annual Report. 735-R-01-004. January 2002.
7. California Department of Pesticide Regulation. February 6, 2003. Sacramento, California.
8. Donaldson D, Kiely T, Grube A. 2002. Pesticides Industry Sales and Usage. 1998 and 1999 Market Estimates. USEPA Office of Pesticide Programs. Washington, D.C.
9. http://www.usda.gov/nass
10. Based on CalEPA Department of Pesticide Regulation Pesticide Use Reports: http://www.cdpr.ca.gov/docs/pur/purmain.htm.
11. Js C, Camann D, Hartge P. 2002. Pesticides in carpet dust and self-reported pesticide use in four areas of the U.S. Ann Epid 12(7):508.
12. Adgate JL, Kukowski A, Stroebel C, et al. 2000. Pesticide storage and use patterns in Minnesota households with children. J Expo Anal Env Epidem 10(2):159-167.
13. Davis JR, Brownson RC, Garcia R. 1992. Family pesticide use in the home, garden, orchard, and yard. Arch Env Contam Toxicol 22:260-6.
14. Graham W. 1996. The Grassman. Can John Greenlee do away with the lawn? The New Yorker, August 19, pp 32-37.

Chapter 2
Exposure to Pesticides

Introduction

Approximately 5 million persons work on farms in the U.S. Hired farm workers account for 2.5 million, of which 1.8 million work in crop agriculture. Since 75 to 80% of conventional pesticide use is in agriculture, these chemicals pose a significant health risk to farm workers and their families. Other farm chemicals are also a potential source of exposure, including fertilizers, solvents, and fuels. Pesticide use inside and outside the home, in offices, schools, day care centers, recreational areas, and other nonagricultural exposures, also poses health risks, especially to children.



Vincent Perez/Artist

Many of the pesticides marketed in the 1940s to 1960s were highly toxic organophosphates, resulting in human poisonings, and severe impacts on birds, bees, fish, and other wildlife. There was inadequate assessment of risk, and the controls of the time purported to "make the worker safe for the workplace".

The assumptions were that most poisonings were a result of misuse, failure to follow label directions, lack of proper training, or failure to use protective clothing and equipment.

Placing blame on pesticide handlers and other poisoned workers ignores other important factors – substandard conditions of agricultural practice, failure to provide and maintain protective clothing and equipment, lack of pesticide use and pesticide illness reporting systems, and not paying attention to potential long term effects of low level exposures not causing apparent illness.

Several decades would go by before minimal changes were made in pesticide law to begin protecting pesticide exposed workers in agriculture. The workplace protections of the 1970 Occupational Safety and Health Act (OSHA) were never applied, since agricultural workers were excluded from OSHA's jurisdiction. Only workers in pesticide factories and formulation. plants are protected by the statute.

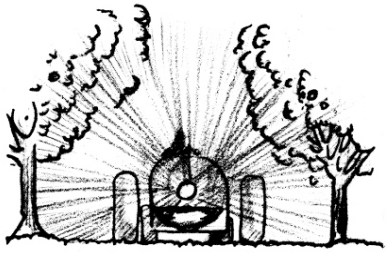
Sources of Exposure

Occupational: The major source of work place exposure to pesticides is in agriculture. The most heavily exposed are workers who mix, load, apply, or otherwise handle the concentrated technical formulations. Farm workers are exposed when cultivating and harvesting crops in fields, nurseries and greenhouses, as well as transporting and handling agricultural commodities in packing houses and storage facilities.

Major non-agricultural exposures are in PCOs (pest control operators), exterminators, and workers applying pesticides to structures, turf, lawns, roadways, and other applications.

Non-occupational: Residents living in or near pesticide use areas are exposed through drift and volatilization from pesticides that deposit on crops, accumulate in soil, and contaminate surface and groundwater.

Drift and other environmental exposure occurs from pesticides applied in both rural and urban areas in agriculture, homes, offices, schools, restaurants, hotels, hospitals, lawns, rights-of-way, parks, sports arenas, golf courses, landscaped urban areas, and almost anywhere humans live and congregate.



Vincent Perez/Artist

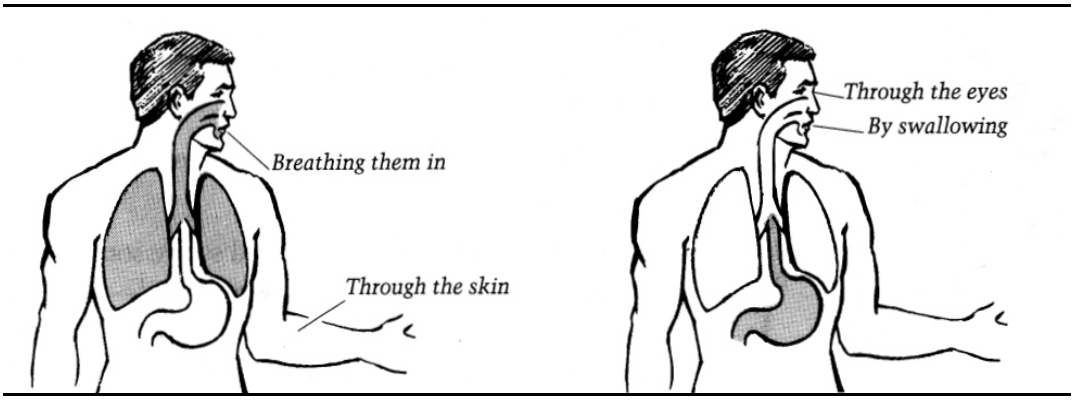
Airblast Sprayer.

Direct exposures occur from use of over-the-counter products for home, lawn, garden, and pets, and personal products used directly on the body as repellents, and for control of lice, scabies and other pests.

How Pesticides Enter the Body

Dermal Exposure: The skin is the largest organ in the body and the major route of absorption of pesticides. If the skin is sweaty, wet, or there is a rash, sore, cut or other skin problem, pesticides will be absorbed more rapidly and in greater amounts. If pesticides are spilled or splashed on the skin and not removed immediately and thoroughly, absorption will continue as long as they are in contact with the skin.

Pesticides are absorbed from contaminated work clothing (see section below on laundering), and can enter the body by walking barefoot on treated surfaces. Children can absorb pesticides from contact with treated pets, lawns, contaminated carpet, upholstery and other surfaces.



Vincent Perez/Artist

Figure 1. How Pesticides Enter the Body

High Skin Absorption Areas: Some areas of the skin absorb pesticides more readily than others. After applying radioactive isotope ^{14}C (carbon 14) labeled parathion, malathion, and carbaryl to the skin, and measuring the amounts of radio labeled pesticides in the urine, it was shown that the scrotum allowed almost total absorption, compared to the forearm. The scalp, angle of the jaw, post-auricular area, and forehead, had four fold greater penetration, and the axilla four to seven fold greater absorption. The palm allowed about the same penetration as the forearm, and the abdomen and dorsum of the hand had twice the penetration[1] (see Figure 2).

Crop Residues: Farm workers can receive significant skin exposure from residues remaining on the foliage of the crops they are cultivating or harvesting – called "dislodgeable foliar residues".

The amount of dislodgeable residue available depends on the decay rate and environmental fate of the particular pesticide formulation, ambient temperature, humidity, rainfall, and other climatic conditions. The degradation rate in general is slower in hot and dry conditions, and more rapid under cooler and wetter conditions. Some pesticides can form more toxic

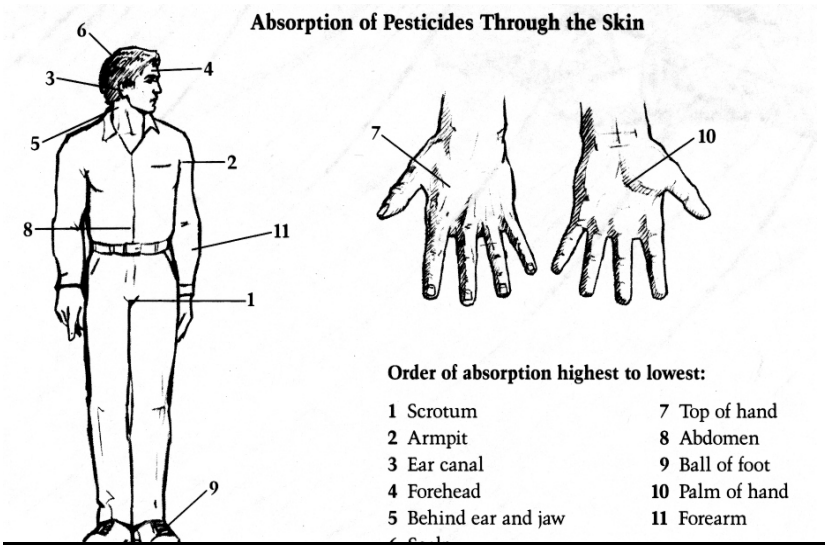


Figure 2. Dermal absorption

Vincent Perez/Artist

products on leaf surfaces . See Chapter 3 for the discussion of reentry poisonings in farm workers.

Major Factors Influencing Pesticide Exposure and Absorption

Type of formulation
Rate of absorption into the body
Duration of exposure
Protective clothing and equipment
Climate (temperature, humidity)
Work Practices

Duff: Workers are also potentially exposed to pesticides residues in contaminated duff – dead leaves, twigs, dust, and other debris under trees and vines in groves, orchards and vineyards.

Dermal Absorption of Vapors: Pesticide vapors can also be absorbed through the skin even though the primary route of absorption is the lungs. This is especially true for workers using masks while exposed to fumigants such as methyl bromide, 1,3-dichloropropene, and sulfuryl fluoride. Standard protective clothing does not protect against such exposure[2,3].

Skin exposure much higher than respiratory:(see Tables for data)
Dermal exposure is much greater than respiratory exposure in workers who handle pesticides and pesticide treated crops. Skin exposure accounted for more than 90% of total body burden in applicators spraying trees and ornamental shrubs; inhalation exposures were below OSHA and NIOSH standards[10.] Hand exposure was the largest contributor to absorption of azinphosmethyl (Guthion) in apple thinners. Use of absorbent gloves to monitor hand exposure grossly exaggerated estimates of potential exposure[4].

Other studies showing greater dermal exposure include: herbicide ground sprayers[5], sprayers of dimethoate[6], omethoate, fenitrothion, and tolclofos-methyl[7], picket flowers treated with propoxur[8], applying zineb/maneb[9], carbaryl, chlorpyrifos, and permethrin[10], fosetyl-Al to ornamentals[11],acephate, benomyl, carbaryl, chlorothalonil, diazinon, and dicofol to urban trees and shrubs[12], commercial disinfectants[13], chlorinated hydrocarbons[14], ethion to citrus[15], lindane seed treatment[16], and mechanical harvesting of chlorothalonil treated tomatoes[17].

Absorption of the insecticide azinphosmethyl (Guthion) in peach pickers was greatest two hours after exposure and reached equilibrium in three hours. The authors cautioned that exposure estimates from shorter intervals would overestimate exposure[18].

Type of equipment affects deposition of pesticides. Hand exposure to ultra-low-volume (ULV) 2,4-D was much higher for workers using tractor-powered sprayers than for knapsack sprayers, whose highest exposure was to the lower legs. Skin exposure to sprayers using hydraulic nozzles was lower than those using controlled droplet equipment. Respiratory exposure was negligible compared to skin in all applications[19].

Inhalation: Even though the respiratory tract is not a major route of pesticide entry into the body compared to the skin, absorption is almost 100% once it enters the deeper air passages in the lungs. The lungs are the major route of absorption of fumigants – pesticides in the form of a gas.

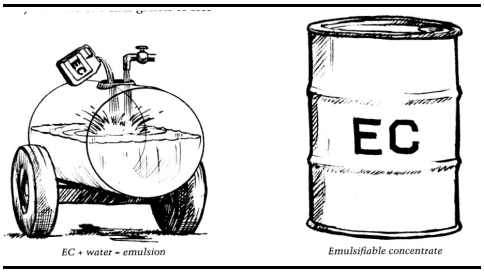
Respirable Particle Size

Less than 10 microns	Reach upper air passages
5 to 10 microns	Reach central bronchial passages
1 to 5 microns	Reach peripheral bronchial passages

How deeply pesticides penetrate the upper airways and the lungs depends on particle size, breathing rate, and the amount of fresh air and ventilation. The smaller the particle, the greater the number of breaths per minute, and the less circulating fresh air, the greater the deposition.

Granules and dusts, and some powders are large enough to be trapped in the nose and upper air passages before they get into the lungs. Gas deposition depends on its solubility in lung tissue. Semivolatile compounds exist as both particles and gases simultaneously.

In laboratory simulations of respiratory exposure to chlorothalonil, a worst-case spill generated about 0.00001% as an aerosol. Assuming a 1% transfer efficiency between the spill and the mixer/loader, these estimates were between 10,000 and 480,000 times less than literature data for respiratory exposure by applicators and harvesters. The inhalation of aerosols from mixing and loading was found to be a minor component of exposure[20].



Vincent Perez/Artist

Figure 4. Emulsifiable concentrates form emulsions when mixed with water and are readily absorbed through the skin.

Ingestion: Swallowing is a major route of exposure for pesticides in accidents and suicide attempts. In the U.S., children under six are most at risk for accidental ingestion (see Chapter 3).

Through the Eyes: Pesticides can enter the body through the eyes. Because blood vessels are close to the surface, pesticides can then get into the blood stream and cause poisoning, but this is rare. Most cases are from splashes and spills in mixer/loader/applicators not wearing goggles, a face shield, or other eye protection.

Factors in Pesticide Absorption

Pesticide exposure and absorption depends on the type of formulation and its rate of absorption, the duration of exposure, type of application equipment and protective clothing, handling practices, work rate, duration of exposure, post application clean up, and training and experience. Application pressure and ventilation conditions affect skin deposition rates and breathing zone contamination[21].

Pesticide Formulations

Pesticide formulations are mixtures of the active ingredient pesticide with inert and other ingredients into the final marketed product; they are important determinants of absorption into the body. Almost all agricultural and commercial use products are sold as the technical concentrated product which is diluted by the spray crew at the time of use. Most home use products are sold already diluted and ready for use.

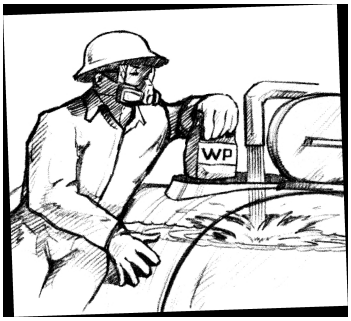
Commercial Formulations: There are four basic types of formulations used in agriculture and commercial pest control – dry, wet, fumigants, and attractants/ repellents.

Dry formulations include dusts, wettable powders, slurries, granules, and pellets. Powders are mixtures of the pesticide with a carrier, usually mineral clay. Powders are smaller in particle size than dusts and granules, and are more hazardous to the handler. Because of severe poisoning episodes in workers handling wettable powders, the State of California requires the more toxic ones to be formulated as water soluble packets that can be put into the spray tank without opening (Figure 3).

Wet or liquid formulations include emulsifiable concentrates, ultra low volume concentrates, flowables, and solutions. Emulsifiable concentrates are formulations in which the pesticide is first dissolved in a petroleum solvent or oil with an emulsifier added so the oil and water will mix. When mixed with water it turns milky (see Figure 4). ECs can be more hazardous than powders and dusts because they are readily absorbed through the skin. Ultra low volume formulations are applied at a very low rate of half a gallon or less per acre. They are highly concentrated containing 80 to 100% of the active ingredient pesticide. They are applied without dilution using special sprayers and are can be very hazardous to the handler.

Fumigants are pesticides in the form of a gas and can be formulated as liquids (e.g. liquid nitrogen), solids (e.g. moth balls) or gases (e.g. sulfuryl fluoride, methyl bromide). Some pesticide fumigants require contact with water to emit toxic gas . Phosphine is released from aluminum, magnesium, and sodium phosphide, and methylisothiocyanate (MITC) from metam-sodium. Fumigants directly enter the lungs where they are rapidly absorbed. They are among the most hazardous of all pesticide formulations.

Attractants/repellents are lures and baits, including pheromones, syrups, and yeasts. They are among the safest of all pesticide formulations.

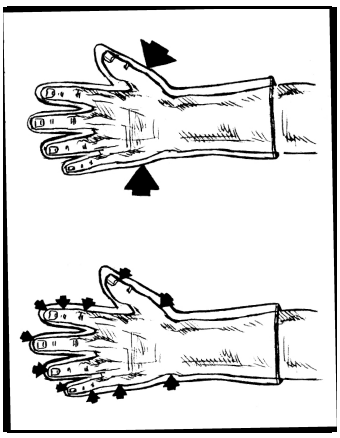


Vincent Perez/Artist

Figure 3. California law requires water soluble packets for the most toxic wettable powders.

Consumer Over-the-Counter Products

Most product sold directly to the public are already mixed and ready to use. In general their concentration is much lower than the technical products used in



Vincent Perez/Artist

Figure 7. Pesticides accumulate on gloves and other protective clothing and equpmen and over time will penetrate any type.

agriculture and commercial pest control. High concentrations requiring dilution are increasingly being marketed for home, lawn, and garden use. The four basic types of formulations sold over the counter are foggers/bombs/aerosols, liquids /sprays, dusts/granules/powders, and baits and traps.

Foggers, bombs and aerosols are designed for maximum penetration and coverage of the area being treated. Residues settle out of the air and contaminate everything they contact. Contaminated floors, carpet, upholstery, drapes, furniture, and any objects in the treated area can become a source of continuing exposure for days, weeks, months, or even years. They often contain toxic inert ingredients, including petroleum distillates and solvents.

Liquids and sprays are potentially less hazardous than foggers, bombs, and aerosols because the spray is more directed and less likely to settle out on everything in the treated area. However volatilization and redeposition can distribute pesticide residues to areas and objects that were not treated, including children's toys

Granules, dusts, and powders: Granules are large, roughly the size of coffee grounds, and are trapped in the upper airways. Dusts and powders are smaller in size, and the hazard depends on concentration and conditions of use. Granules and pellets are often very hazardous to wildlife and pets which mistake them for seed or food.

Baits and traps are the least toxic type of formulation and some traps are essentially nontoxic. Most baits do not give off harmful vapors, mists, sprays, or residues that contaminate the entire treated area. The pesticide stays in the container it comes in, relying on the pest coming to the bait or trap. They can be hazardous to children, pets, and wildlife if not used properly.

Work Practices, Protective Clothing and Equipment: (see Tables for data)
Pesticides on farms can be applied by the farmers themselves, by crews of their own workers, by commercial crop dusters, or some combination. Most workers on farm spray crews are not certified, but work "under the supervision of" a certified applicator as allowed by the FIFRA law. Many of the farm workers who mix, load, and apply pesticides have low reading skills, or may not be literate in English.

Gloves, masks, and other protective clothing and equipment may be unavailable, unfit, or improperly maintained. Coveralls may be worn all season and rarely or ever laundered. The same mask filters, which must be changed daily at a minimum, may be used for an entire season of spraying.

Many chemical protective clothing products in current use are inadequate for worker protection. None of the garments tested protected greenhouse workers from contact with treated foliage under the use conditions observed[22].

An airblast spray crew showed exposure in areas covered by protective garments in 24 of the 25 workers. The order of protection from greatest to least was non-woven coverall > woven coverall > work shirt[23].

Farmers applying insecticides to animals were protected against low but not high concentrations by their protective clothing. The highest exposures were related to poor work practices, leaking equipment, contact with wet animals or fences, and back splash[24]. Other studies also find dramatic evidence of protective clothing failures[25,26].

Table 1
Survey of Iowa and North Carolina
Farm Pesticide Applicators

Home within 50 yards of mixing areas	21%
Store pesticides in home	27%
Wash work clothing with family laundry	94%
Wives work in the fields	51%
Wives mixed or applied pesticides	40%
Children ≥11 do farm chores	> 50%

A NIOSH (National Institute Occupational Safety and

Health) health hazard evaluations at two greenhouses in California found poor work practices and limited understanding of proper use and care of personal protective equipment, especially respirators. Neither site had a respirator program and when respirators were used, it was often incorrectly. Nor were there cartridge replacement criteria or shower facilities for emergency situations[27, 28].

Sixteen percent of farmers in the Agricultural Health Study reported a high pesticide exposure event (HPEE), defined as "an incident or experience while using any pesticide which caused an unusually high personal exposure ". Work practices more common among applicators with an HPEE included: a delay in changing work clothing, delay in washing up after pesticide application, mixing pesticide application clothing with the family wash, washing up inside the house after application, applying pesticides within 50 yards of their well, and storing pesticides in the home. HPEE was also associated with self-repair of application equipment [29,30] (see Table 1). The authors concluded that current practices minimizing exposure were not sufficient for acutely toxic or irritating chemicals[31].

Aerial application of paraquat to cotton study in California found dermal and respiratory exposure of pilots, flaggers and a mixer-loader to be low. Skin exposure in flaggers was 480% greater than in the pilot and the mixer/loader, and a factor of 19 less than the TLV (threshold limit value).Respirable paraquat was not detected in the breathing zone of any worker, and drift concentrations decreased with increasing distance downwind of the spray application[32].

A study of captan exposure in a farm family found small differences between the fruit grower and his son, but the wife's exposure was two to three times lower[33]. In an airblast spray crew applying malathion, applicators' exposure was more than three times higher than mixers[6].

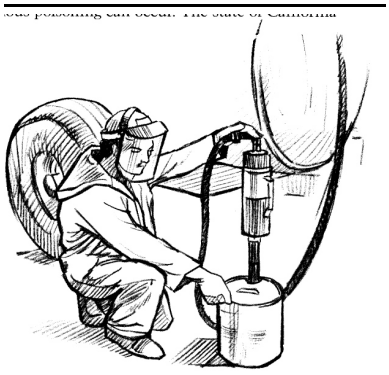
Greenhouse Workers: (Tables 4-A and 4-B)
Greenhouse applicators work in enclosed spaces with variable ventilation and humidity. Pesticides are applied by thermal fogging, hand gunning and drenching. Most worker exposure occurs during hand gunning, which involves spraying foliage under low to high pressure. Drenching is a chemical treatment of the roots of plants using a coarse stream of water under low pressure. Thermal fogging has the highest potential for exposure, but is performed by trained and experienced workers, using extensive precautions and protective clothing and equipment. Contact with treated foliage is a continuing source of exposure for other workers.

A study in Italy found the skin, especially the hands, to be the major source of exposure to greenhouse workers. Gloves must always be used and changed frequently to maintain worker protection. The amount of omethoate absorbed by one worker was more than 45 times the acceptable daily intake (ADI), but the ADI for fenitrothion and tolclofos-methyl were never exceeded[11].

A fluorescent tracer study in Florida of experienced and inexperienced greenhouse applicators, showed that in hand gunners the experienced applicators had a seven fold decrease in total body deposition when the ventilation system was on, compared to the inexperienced applicators who had a 10 to 30 fold increase in deposition. When the ventilation system was off there was no difference between them. It was found that the experienced applicators stay upwind from the drift[34].

Tractor applications: The best protections for ground applicators are closed windows and carbon filtered air, but most work in open tractors without shielding, and truck cabs with open windows. Closing windows significantly reduces exposure but is impractical because temperature inside the cab becomes quite high. Fitting tractors with a metal cage canopy provides some protection, as does closing the window on the driver's side, which also prevents sprayed wet branches from contacting the driver[35].

Even when the pesticide label requires closed cabs, it usually does not require that the cab be equipped with a carbon filter or air conditioning, making open windows a necessity in hot weather.



Vincent Perez/Artist
Figure 5. A mixer/loader using a closed system

Closed Systems: Closed mixing and loading is the transfer of chemicals

with no direct exposure of any handler to the pesticide[36]. California requires closed systems for pesticide in EPA Toxicity Categories I and II (see Chapter 3 for explanation of these categories).

Non-agricultural handlers: Similar conditions exist in commercial pest control. As in agriculture, most workers for extermination, lawn care, and other pest control companies, are not certified but work under the supervision of a certified applicator. Turnover is high, training is not always optimal. In Australia applicators doing home pest control with organochlorine pesticides in 1972, and chlorpyrifos in 2001were using respirators in poor condition, inadequate protective clothing, poor work practices, and had a high frequency of splashes and spills onto the body[37,38.]

A statewide telephone survey of California pet handlers in veterinary clinics, pet stores, kennels, grooming shops, and animal control facilities, found that using protective clothing and equipment and good work practices prevented signs and symptoms of overexposure[39].

How Pesticide Exposure is Assessed

Passive dosimetry: Beginning in the 1950s, the use of absorbent cotton patches on workers' skin, work clothes and protective garments, called passive dosimetry, was used to assess worker exposure to pesticides. The severe limitation of this method is that it does not measure how much of the pesticides is actually absorbed into the body [40]. Passive dosimetry is a good method for assessing penetration of pesticides through gloves and protective clothing fabrics, and is still used for this purpose.

Surrogate measures such as acres planted and pounds of use estimates are not reliable indicators of pesticide exposure. Agreement between farmer reports and actual use found a 70 to 90% agreement for ever/never use of specific pesticides, but only 50-60% agreement for duration, frequency, or decade of first use[41] .

Video Imaging (VITAE): A method which more accurately measures how much pesticide is absorbed through the skin was developed by Fenske and coworkers in the 1980s. A fluorescent tracer whitening agent[a] is added to the pesticide being applied. A television camera interfaced with a computer is then used to visualize and quantify skin deposition patterns. The system, called VITAE (video imaging technique for assessing exposure) is a powerful educational tool in convincing applicators to adopt safer application methods and to use protective equipment and clothing no matter how brief the exposure[42]. Since the tracer penetration is slightly less efficient than the pesticide, and skin deposition and fabric penetration of the tracer and the pesticide are highly correlated, there are no false positives[43,44,45,46]. The latest second generation video techniques found that skin pigmentation had a substantial effect on the fluorescence response, which could be represented mathematically[47]. The need to introduce a chemical tracer into production processes limits the use of this method.

Penetration of protective clothing made of rubber, tyvek, cotton, cotton/polyester blend, and nylon by the insecticides deltamethrin, endosulfan, and pirimicarb, using fluorescent tracers found no consistent relationships. Trace levels were found on four tyvek samples treated with deltamethrin, and one with endosulfan. A small amount of deltamethrin was found beneath the blended material and none on cotton sample. A relatively constant penetration ratio for deltamethrin was seen for the blended material. Penetration ratios for pirimicarb were inconsistent. The amount of tracer which penetrated all three materials was much lower for pirimicarb compared with the other two pesticides[48].

Nonuniform deposition of pesticide mixtures in Canadian pirimicarb applicators using fluorescent tracers showed that the assumption of uniform deposition with the dermal patch passive dosimetry method was incorrect. Exposure estimates were highly correlated with urinary metabolites, $r^2 = 0.93$[39].

Residential Home, Lawn Exposures: Table 6

A study of residential application of chlorpyrifos found that ventilation from open doors or windows reduced air concentrations substantially. Air concentrations were also greater near the floor than at one meter above the floor. Residues recovered from treated surfaces decreased by 60-70% over 24 hours, while residues on untreated surfaces increased 200-300%[49].

[a] Earlier studies used 4-methyl-7-diethyl-aminocoumarin as the fluorescent tracer. 2,2'-(2,5-thiophenediyl)- bis(5-tert-butylbenzoxazole) is now preferred.

An EPA study of indoor and outdoor home exposures – Non-Occupational Pesticide Exposure Study (NOPES) – sampled residents for 24 hours using personal air monitors for 32 pesticides between 1986 and 1988. Springfield /Chicopee, Massachusetts was selected as an area of low household pesticide use, and Jacksonville, Florida as an area of high household pesticide use. Indoor and personal air concentrations were higher in Jacksonville than Springfield/Chicopee, and were highest in summer, lower in spring, and lowest in winter. Indoor levels were usually much higher than outdoor air concentrations. Inhalation risks were uncertain for termiticides (depending on rates of degradation), and negligible for other pesticides[50].

A study of minority black and Dominican women in New York City found that 85% used pesticides at home during pregnancy. Nine percent used illegal "street " pesticides Tempo (cyfluthrin for cockroaches, and Tres Pasitos (aldicarb) for rodent control. Fifty-four percent of can sprays users, 50% of boric acid users, 48% of sticky trap users, and 45% of exterminator users reported use once a month or more. Personal air sampling for 48 hours during the third trimester of pregnancy found eight pesticides present a greater than the level of detection, in 45% or more, and four – chlorpyrifos, diazinon, piperonyl butoxide, ortho-phenylphenol – present in 100%[51].

Ambient air from the basement, kitchen, and one bedroom of 19 homes treated for subterranean termites found very low levels of chlordane and heptachlor during application, and 24 hours, one week, and monthly for 6 months after application[52].

Absorption of disodium octaborate tetrahydrate from nylon carpet was measured by using volunteers in a 20-minute Jazzercise routine on the treated carpet. Boron clearance in a 24 hour urine sample found no difference between those wearing bathing suits versus those wearing whole-body, cotton dosimeter socks, union suits, and gloves[53].

A Dow study of chlorpyrifos absorption in adult residents in three houses for 10 days after crack and crevice treatment found that 3,5,6-trichloropyridinol (3,5,6-TCPy) was the major metabolite in the urine. Ten-day cumulative deposit of residues on living area floors and non-target surfaces was low, and no significant decrease in cholinesterase was found[54].

Five volunteers who ingested chlorpyrifos, had it applied to their skin for 8 hours four week later. The half life for elimination in the urine was 15.5 hours for the oral dose, and 30 hours for the skin dose. A mean of 93% (range 55 to 115%) of the oral dose was recovered in the urine and 1% of the dermal dose; 53% of the dermal dose was recovered from the skin surface. There was no significant decrease in plasma or red blood cell cholinesterase[55]

A study of two different techniques found that the foliar wipe method removed an average of 1.5% of chlorpyrifos from treated blue grass and 6.1% of tracer one to three hours after treatment. The foliar wash method recovered more, an average of 4.0% of chlorpyrirfos, and 10.5% of tracer. This means that the method used is very important since one could produce higher estimates of potential exposure if used as a turf contact-transfer factor[56].

One reviewer summarizing chlorpyrifos biological monitoring data found chronic aggregate nonoccupational exposures in adults of 0.0002 mg/kg-day, and in infants and small children of 0.0005 mg/kg-day. These are an order of magnitude less than exposure estimates from standard methods. Biological monitoring data of cumulative exposure to all organophosphate pesticides ranged from 0.0003 mg/kg-day in adults to 0.003 mg/kg-day in children. The author concluded that the risk of aggregate, nonoccupational exposure to chlorpyrifos has been overstated by more than a 1000-fold[57].

Biological Monitoring of Exposure

The best measure of pesticides exposure and absorption is the actual level of residues and metabolites in body fluids and tissues. Monitoring of workers and the general population can determine low levels of exposure that do not produce signs and symptoms of illness, or have any measurable effect on physiological responses.

Pesticides in Urine: The most readily available body fluid is urine; it does not require an invasive procedure such as venipuncture to obtain blood, or biopsy to obtain fat and other tissues. Although the most accurate measurement of pesticides in urine requires collection over a 24 hour period, most specimens are one time "spot" samples. To correct for volume, spot samples are "creatinine adjusted", since excretion of this breakdown product of protein metabolism

is constant over 24 hours, and easy to measure. Pesticide levels are then reported "per gram of creatinine". The assumption of the constancy of creatinine excretion has been questioned, especially for children[58].

Many organophosphates degrade to dialkylphosphate (DAP) metabolites that are excreted in the urine. DAPs could be from one or more of any number of organophosphate insecticides (see Appendix C). DAPs are not toxic and do not inhibit cholinesterase. They are of no value in the diagnosis and management of acute organophosphate poisoning. They are rapidly excreted and represent recent exposure, within the past two or three days at most.. They are useful for monitoring and documenting exposure since they are detectable in urine at levels too low to cause cholinesterase depression or symptoms of poisoning. It is not a routine test in hospital laboratories.

Urinary DAPs are frequently done in exposure assessment in both agricultural workers and the general public. A recent study showed that pesticides and their metabolites are widely found in the urine and blood of the general public who do not have occupational exposure to pesticides. One of the more striking findings was the large difference in DDE, the most prevalent metabolite of DDT, which was 3.1 times higher in Mexican Americans compared to whites, and 2.2 times higher compared to blacks (see Table 7)[59].

Storage and Disposal: Conditions under which toxic pesticides are stored, transported, used, and disposed of are rarely optimal, and poorly regulated. An early survey of agricultural sprayers in the Mississippi Delta found that 70% disposed of pesticide containers indiscriminately, 10% recycled them, 10% utilized low land area for dumping, and 8% used public dumpsters[60]. Household pesticide use is also a source of environmental and ground water contamination, as well as land fills[61].

Laundering Recommendations for Pesticide Handlers

1. Keep pesticide clothing separate from family clothes before and during laundering.
2. Pre-rinse or pre-soak clothing and discard rinse or soak water.
3. Use hot water to wash, cold to rinse.
4. Use a heavy-duty detergent
5. Wash only a few items at a time. High water volume enhances residue removal, so do not overcrowd washer.
6. Use the highest water level setting, even for small loads.
7. Use the longest wash time cycle – at least 10 to 12 minutes.
8. Never use sudsaver feature.
9. Do another complete wash cycle before drying.
10. If the second washing does not remove stains or odor, discard the clothes.
11. If possible, hang clothes to dry in the sun. Sun helps degrade some pesticides.
12. Before laundering family clothes run the washer through a complete cycle without clothes . Use hot water and detergent.

Other Information

1. Ammonia is not effective in residue removal.
2. A three hour soak in chlorine bleach solution may help remove chlorpyrifos.
3. Fabric softeners neither help nor hinder residue removal.
4. Solvent-based pre-treatment sprays help remove oil-based formulations.
5. Salt (1 cup per load) helps remove paraquat, but not other pesticides.
6. Starch may help prevent pesticides from reaching the skin. Heavy starching of lower

Laundering Work Clothing:
Wearing clean clothing every day is important in protecting workers from pesticides[62,63,64]. This is a neglected area of worker protection, and most farm employers do not provide clean outer clothing for their workers. One study of pesticide handlers found that changing daily to freshly laundered 100% cotton coveralls provided significantly greater protection than regular clothing and the use of respirators[65].

Pesticide residues transfer from contaminated clothing to other clothing if they are laundered together. The hotter the water, the greater the transfer[66,67]. A study of 2,4-D removal from denim found that up to 2% was transferred in laundering to non-contaminated fabric[68]. A home laundering study found that a mixture of three pesticides was harder to remove than a single pesticide, and all were transferred to uncontaminated clothing[64]. A recent survey of Iowa and North Carolina farmer applicators in the Agricultural Health Study found that 94% mixed contaminated work clothing in with the family wash[69].

Higher water temperature removes much higher amount of residue[70], and pre-rinsing increases removal. High water volume is more important than agitation in removing residues[71]. Several studies show that ammonia is not effective in residue removal, and may even hinder removal. Pre-rinsing or pre-soaking decreases residue removal. Two washes remove more than a single wash.

Heavily soiled clothing which should be discarded is often reused[72]. The more concentrated the pesticide the higher amount of residue is left in clothing after laundering. A study of methyl parathion removal from denim after laundering found that 96% of a 0.25-0.50% formulation was removed, 92% of a 1% formulation, but only 20% of a 54% concentrate. The concentration also affected how many launderings it took to remove the residue. For

formulations less than 2%, it took three washings to completely remove the residues. For the 54% formulation 67% of the residue was still present after ten launderings, and the fabric killed 100% of exposed cockroaches within 24 hours

Some pesticides are harder to remove than others, and type of fabric can also make a difference. In general removal is easier from cotton than from synthetic fabric. A study of carbofuran and methomyl removal from cotton and polyester fabric in a household automatic washing machine found higher amount of methomyl residues remaining in the polyester. After 72 hours the laundered fabric caused 40% mortality in exposed rats[73]. Another study found that captan, diazinon and malathion were easier to remove than dicofol, endosulfan, cypermethrin and permethrin. When noncontaminated fabric was laundered with contaminated fabric, significant amounts of organochlorine and pyrethroid pesticides were transferred[63].

Tables follow.

Table 2-A
Agricultural Pesticide Handlers (Mixers, Loaders, Applicators - MLAs)
by Specific Pesticide

Chlorothalonil simulated aerosol exposure[20]	
Aerosol generation	2.1- 5.3 ng/l
Atomization through a hollow cone	354 ng/l
Atomization through flat fan nozzles	96 ng/l
Male worker inhaling 29 l/min	0.32-0.78 ng
Estimates vs respiratory data in literature	10- 480K less
Iinhalation aerosols percentage exposure	Minor
Chlorpyrifos, carbaryl, permethrin MLAs[21]	
Primary source of skin contamination	Hands
Penetration cotton polyester blend fabric	16-43%
Respiratory toxic dose per hour	0.01-0.03%
Cypermethrin ULV dermal exposure[74]	
Pilots mean absorption 8 hours	1.07(.26- 2.7) mg
Mixer/loaders mean absorption 8 hours	10.5 (2.5-23) mg
Pilots - absorption by hands	67%
Mixer/loaders absorp. arms, trunk, hands	37, 24, 17%
Skin exposure mean - pilots	0.67 mg/day
Skin exposure mean - mixer/loaders	2.43 mg/day
Urine metabolites	46-78 ug
2,4-D dermal exposure mix/load vs spray[29]	Highest
Hydraulic nozzles equip. vs knapsack	Lowest
Sprayer controlled-droplet equipment	Intermediate
Highest exposure all operations	Hands
Highest exposure knapsack sprayers	Lower legs
Respiratory vs dermal exposure	Negligible
Dimethoate, malathion applicators[75]	
Operator exposure levels	68 mL/hr
Assistant exposure	25 mL/hr
EPTC mixer/loader/applicators[76]	
Total dose 75 kg man 120 acres of soil	5.6 mg/day
Urine metabolites reduced dose	.74-.147ppm/day
Margin of safety increased from	68 to 34
Fenamiphos mixer/loader/applicators[77]	
Inhalations less than limit of detection	< 0.001 mg/hr
Hands dermal exposure	Highest
Malathion applicators' protective clothing[7]	
Coveralls 65-35 cotton polyester blend	7.2 mg/cm^2
Work shirts 50-50 cotton polyester blend	11 mg/cm^2.
Hands mixers 41% total exposure	138 ug
Hands applicators 13% total exposure	58 ug
Mancozeb air-dispersed farm exposure[78]	57.2 ug/m^3
ETU[(a)] urine 3 cases > LOD[(b)] mg/g creat.	2.9, 2.3, 4.4
Manganese before/after ug/g cr	0.32 / 0.53
Multiple pest. (n=40) dose estimates[©)] MLAs[79]	
Exceeded 1% of estimated human LD_{50}	25%
Estimated % of human LD_{50}	< .0001-48
Exceeded RfD	52%
Lifetime daily dose of EPA RfD	0.1-114,000%
Lifetime cancer risks per million	1- 1700
Estimates for 12 of 13 pesticides	>1 per million
Paraquat application to cotton in California[32]	
Skin absorption in pilots per hour	0.05 mg
Skin absorption in flaggers per hour	2.39 mg/h
Respirable paraquat in breathing zone	Not dectected
Droplets in respirable range downwind[(e)]	0.95-1.96%
Parathion handlers in Florida[80]	
Careful spraymen handled daily	10 lbs
p-Nitrophenol urinary metabolite	0. 8 ppm
Careless spraymen handled daily	11 lbs
p-Nitrophenol urinary metabolite	4. 3 ppm
Absenteeism careless group	71%
Pyrethroid ULV manual sprayers[37]	
Hand-held vs aerial applicators	1,000 times

(a) Ethylene thiourea, a metabolite of maneb.
(b) Limit of detection.
©) Compared to LD_{50} (acute) and reference dose (RfD) (chronic).
(d) Threshold limit value.

Table 2-B
Agricultural Pesticide Handlers (Mixers, Loaders, Applicators - MLAs)
by Type of Work or Crop

Mixer/loaders California[81]	
Water-soluble packet vs closed system	> protection
Skin route of exposure	87-95% of total
Orange grove airblast spray crews[82]	
Hand exposures	0- 329 ug
Head exposures	39- 281 ug
Palm vs backs of hands	2.5 times >
Mixer exposure vs applicators	4 times >
Orange grove airblast spray crews Florida[15]	
Respiratory exposure	< 1%
Hand exposure applicators	42%
Hand exposure loaders	76%
Orchard airblast spray crews[83]	
Skin deposition upper body	4-22%
Ventral segment forearm for mixer	Highest
Front vs side of head, applicators	3 x higher
Front vs side of head, mixers	3 x lower
Vineyard MLAs clothing deposit ng/cm[84]	0.43-0.63
Air blast vs. hooded sprayer	Higher
Neck, shoulder, upper arm	Highest

Table 3
Farm Worker Exposure

California female strawberry harvesters[85]	
No gloves clearance THPI[(a)]ug/person/day	5.3 (.4-13.8)
Latex gloves clearance ug/p/d	2.0 (.9-4.3)
Avid glove retention reduced dose	38%
California strawberry pickers skin exposure[86]	
Captan - no corr. with productivity	39 mg/hr/p
Benomyl - pos. corr. with productivity	5.4 mg/hr/p
Florida citrus workers [(b)87]	
DEP detection harvesters	43%
DEP and DETP levels	02 -.04 ppm
DAP levels and symptoms	No assoc.
Iowa, North Carolina[(c)] applicator's meal[88]	
Pesticides being applied	Incr. (20 ppb)
Dieldrin one Iowa farm	Persistent
Drinking water samples	None found

Texas reentry cotton fields ULV malathion[89]	
2 hours after application	4.34 mg
24 hours after application	10.09 mg
Amount methyl parathion	4% or less
Texas migrant farm workers[90]	
Mirex	1.8 ppb
DDT	1.0 ppb
Trans-nonachlor	0.7 ppb
WA apple thinners[(d)] hand exposure[91]	
Using gloves 2.4-fold overestimate	6.48 mg/hr
Handwash	2.7 mg/hr
Wipe methods 10-fold underestimate	0.28 mg/hr

(a) Tetrahydrophalimide a metabolite of captan. **(b)** 6 days after application of azinphosmethyl (Guthion). **]c]** Agricultural Health Study, 6 farms **(d)** 26 farm, 22 farmworker, 11 nonfarm families within 200 ft apple / pear orchard, vs nonfarm ¼ mile or more. Azinphosmethyl, chlorpyrifos, parathion, phosmet.

Table 4-A
Greenhouse and Nursery Workers - by Specific Pesticide

Dimethoate sprayiers[6]	
Dermal exposure mean	914 mg/day
Forearms/hands	84%
Back of the neck	Least
Respiratory exposure	17 mg/day
Maximum dose	18.2 mg/day
Omethoate, toclofos, fenitrothion[7]	
Respiratory exposure omethoate	4.5 ± 8.4%
Tolclofos-methyl	9.9 ± 10.0%
Fenitrothion	49.5 ± 26.6%
Omethoate 1 worker > 45 times ADI	1.4 nml/kg bwt
Tolclofos-methyl ADI not exceeded	212 nml/kg bwt
Fenitrothion exposure[92]	
Respiratory dose 1st day- Monday	94.7%
3rd day- Wednesday	93.1%
5th day- Friday	91.5%
DMP + DMTP 1st day- Monday	245 nml/g cr
Controls	45.5-8 nml/g cr
3rd day- Wednesday	174.0 (2.0)
Controls	17.3- 27.1
5th day- Friday	354.4 (1.6)
Controls	9.7- 19.1
Total estimated absorbed doses	None > ADI

	Mixers	**Appls**
Fosetyl-Al applicators[11]		
Respiratory ug/m^3 7- 9%	3.8-132	6.5- 42
Face and neck 30 to 40%	327 ug	111ug
Forearm exposure	145ug	125ug
Hands wearing gloves 6%	Low	Low
Other parts 50-60%	Lower	Lower
Glyphosate nursery seedlings[93]		
Hand wash positive for glyphosate	1 of 78	
Scouts hand wash positive	1 of 23	
Ankle and thigh exposure	Highest	
Daily total urine 12 consec. weeks	Not detected[(b)]	
Malathion sprayers[94]		
Hand held low pressure sprayer.	25.37 ml/h (.05%)	
Hand held high pressure	35.8 ml/h, (.07%)	
Knapsack applications	160.76 (.09 %)	
Hand lance tractor-gen	283.45 ml/h (.19%)	
Zineb, maneb exposure sprayers[9]		
Dermal estimated exposure	99% of total	
Inhal. low press. knapsack	0.07, 0.09 ml/h	

(a) 2-isopropoxyphenol, a metabolite of propoxur.
(b) Limit of detection 0.01 ug/ml. Authors attribute low levels to rainfall, irrigation as needed, normal field dissipation avenues, worker training.

Table 4-B
Greenhouse and Nursery Workers - by Type of Work or Crop

Greenhouse sprayers[42]		Covariation respiratory/dermal	r = 0.85
Carelessness low-vol. appls	Highest level	Dermal exposure	> 80%
Deposition on body parts	Not uniform	Rose cutters/sorters reentry exposure[96]	
Brief exposure no protection	High levels	Hands/forearms abamectin	13 ug/h
Carnation cutters[95]		Ddodemorph	1.8 mg/h
Dermal exposure gm/work time	10.1 mg/hr	Bupirimate	2.2 mg/h
Sorting/bundling flowers	7.3 mg/hr	Abamectin transfer factor	1,200 cm^2/h
Air after dusting pesticide	0.07 mg/m3	Ddodemorph	4,550 cm^2/h
Same area after spraying	0.049 mg/m3	Bupirimate	2400 cm^2/h
Re-entry after dusting	High	Seedling production workers[97]	
Carnation cutters[8]		Dislodgeable samples positive	8.3%
Propoxur dermal exposure	0.2-46 mg	Patch samples positive	3.2%
Respiratory	3-278 ug	Handrinse samples positive	2.9%
IPP[(a)] urine 24 hr dermal expos.	r=0.95	Urine positive 42 of 3,134	1.3%
Respiratory exposure	r=0.84	(11 benomyl,13 bifenox,18 carbaryl)	

Table 5
Exterminators, Pest Control Operators (PCOs), other Commercial Applicators

Australia chlorpyrifos applicators[38]		US Florida p,p'-DDE blood levels workers[100]	
Cotton gloves under gloves mg/h^{-1}	2.4 (.12-86)	Floral sprayers	< 7ppb
Cotton overall over clothing mg/h^{-1}	11.1 (.2-42)	Lawn sprayers	< 7ppb
Patches taped to skin mg/h^{-1}	0.04 (.01-4.7)	Structural PCOs	< 7ppb
Inhalation concentration ug $m^{(-3)}$	5.7(0.7-219)	Non-whites vs whites	Higher
Breathing air corr. ambient temp.	p < 0.05	US Mil lawn care applicator deposition[101]	
Japan chlorpyrifos termite workers[98]		Lower legs	59%
Air under floor 10 times > TLV[(a)]	1.7-2.3 mg/m^3	Hands	28%
Deposition under floor, crawl space	Highest	US New Jersey chlorpyrifos termiticide[102]	
Right forearm deposition	12 ug/cm^2	Total dermal exposure average	5.94 mg/hr
Left knee deposition	10 ug/cm^2	Estimated absorbed dose 73% dermal	9.5 ug/kg/d
Rright knee deposition	9 ug/cm^2	Percent to upper legs / forearms	38% / 34%
Face deposition	5 ug/cm^2	Accidents 2 of 4 applications	Highest levels
Neck adhesion	High	3,5,6-TCPy 72 hr urine detections	100%
Penetration work clothing	40%	US Termite control applications[52]	
UK Timber and masonry biocide treatment[99]		Chlordane exposure	2.54 ug/kg/h
Spray concent. vs sprayer intentions	Sig diff	Heptachlor exposure	1.88 ug/kg/h
Coveralls - median vs highest	30 - fold diff.	US chemical disinfectant applicators[(b)13]	
Median deposition mg/min	209 (27-6550)	Airborne exposure very low	< LOD
Contamination beneath coveralls	95%	Mean skin dose per task	0.1-26 mg
Contamination beneath overall	5%	Equivalent dose applied mixture	0.1 - 2.7 g
Deposition legs, arms, torso, head	75,11,12,2%		
Hands gloves 89%- med.mg/min	5.78 (.23-358)		
Socks by spray 78%-median mg/mi	2.08 (12-260)		
Inhalation exposure - median mg/m3	53.5 TWA[c]		
Coverall deposition marked increase	100 psi		

(a) Threshold Limit Value for chlorpyrifos 0.2 mg/m^3. Air above the floor close to the TLV..
(b) To floors, walls, other hard surfaces, or carpeting by high or low- pressure spray, mopping, wiping, or aerosol spray.
(c) TWA - time weighted average 4.33-1320 mg/m^3.

Table 6
Home, Lawn, Other Environmental Exposure - Adults

Borate carpet treatment[53]	Mean mg/gr creat
Urinary boron direct skin contact	1.33
Urinary boron protected skin	1.26
Chlorpyrifos preg.♀ personal air (range)[51]	21.1 (0.7-193) ng/m^3
Chlorpyrifos air level crack/crevice[54]	2.3 ug/m^3
Within 10 days of treatment	0.1 - 0.3
Carpet residues	< LOD[(a)]1.6 ug/m^2
Hard plastic balls d prior	< 6.5 ug/m^2
Untreated surface over 10 d	< 2.3 ug/100 cr
Living area floor 2 hr post	< 9.9 ug/100 cr
Urine 3,5,6-TCPy[(b)] adults	No increase
Chlorpyrifos bluegrass turf appl.1-3 h[56]	Amt. Recovered
Foliar wipe technique	0.5 ug/cm^2 (1.5%)
Foliar wash technique	1.3 ug/cm^2 (4%)
Chlorpyrifos / tracer ratio	4.6 sig > wipe
Chlorpyrifos exposure adults[57]	0.0002 mg/kg-d
Cumulative OPs	0.0003 mg/kg-d
Chlorpyrifos air concentration[49]	> near floor
Treated surfaces after 24 h	60-70% decr.
Untreated surfaces after 24 h	200-300% incr.
Chlorpyrifos oral/skin 8h 2 wks[[c]103]	1 mg /28.6 mg
Oral dose half-life	15.5 hours
Dermal dose half-life	30 hours
Oral dose urine recovery	93% (55-115%)
Dermal dose urine recovery	1%
Dermal dose skin recovery	(53%
Skin absorption rate	456 ng/cm^2
Chlorpyrifos skin 24 h after	Most still present
Solvent vehicle	Affects penetrat.
Deet Nat.Park Serv. employees urine[104]	< 0.18-5.69 ug/ml
Diazinon preg. ♀personal air[1] ng/m^3	159 range 2.0-6,010
NOPES[(e)] indoor/personal air[57]	Higher Florida
Summer	Highest levels
Winter	Lowest levels
Indoor vs outdoor	Usually much >
Inhalation risk termiticides	Uncertain
Organochlorines Love Canal[105]	
HCB, β-HCH	0.1 to 26 ppb
Other compounds not detected or	sub ppb levels
Organochlorines termite applications[58]	
Resident's exposure chlordane	< 0.69 ug/m^3
Resident's exposure heptachlor	2.86 ug/m^3
o-Phenylphenol preg.♀pers. air (range)[51]	35 (5.7-3)ng/m^3
PCP[(f)] log home residents levels ppb[106]	420 (69-1,340)
Control homes in ppb	40 (15-7)
PBO[(g)] preg. ♀personal air(range)[51]	1.1 (ND-11.1) ng/m^3
Propoxur preg. ♀ personal air (range)[51]	85 (3.9-1,380)ng/m^3
VOC[(h)] air levels from foggers highest[107]	328 mg/m3,
VOC from EC sprays lowest	20.5 mg/m3
After 3 hours ventilation	75-80% decrease

(a) Limit of detection, the smallest amount found by the method used. **(b)** 3,5-6-trichloropyridinol, chlorpyrifos metabolite. **[c]** Based on urinary dialkyphosphates, organophosphate biomarkers. Study done in volunteers. (**d)** From closed house ventilation and the opening and closing of doors and windows. **(e)** Non-occupational Environmental Pesticide Study, samples 49-72 persons, Jacksonville, Fla and Springfield/Chicopee, Mass, summer 1986 (Jacksonville), spring 1987, winter 1988 for 32 pesticides primarily by inhalation. **(f)** Pentachlorophenol wood preservative. **(g)** Piperonyl butoxide. **(h)** Volatile organic compounds.

Table 7
Pesticide Residues in Blood and Urine – Adults Geometric Mean by Age, Sex, and Race
(from National Health and Nutrition Examination Survey (NHANES) 1999-2000)[20]

Chemical	Units	All ages	Age 20-59	Male	Fem-ale	Mex-Amer	Black	White
DMTP Metabolite of organophosphate pesticides	ug/g creat.	1.64	1.47	1.61	1.66	1.6	1.45	1.68
DEP Metabolite of organophosphate pesticides	ug/g creat.	0.92	0.883	0.86	1	1.09	1.07	0.931
3,5,6-TCPy trichloropyridinol, chlorpyrifos (Dursban)	ug/g creat	1.58	1.41	1.48.	1.69	1.46	1.47	1.66
beta-HCH Hexachlorcyclohexane (in lindane)	ng/g lipid	15.0	16.9	NC*	17.2	25.9	NC*	NC*
p.p'-DDE metabolite of DDT	ng/g lipid	260	297	249	270	674	295	217
T**NA** trans-Nonachlor, a metabolite of chlordane	ng/g lipid	18.3	20.8	17.7	18.8	NC*	20.3	19.1
2,4-6 TCP trichlorophenol[a]	ug/g creat.	2.54	2.32	2.24	2.88	2.43	2.13	2.59
1-Naphthol metabolite of carbaryl[b]	ug/g creat.	1.52	1.64	1.33	1.73	1.34	1.22	1.6
2-Naphthol naphthalene metabolite[©)]	ug/g creat.	0.42	0.474	0.39	0.46	0.5	0.543	NC*
2,5-DCP 2,5-dichlorophenol, paradichlorobenzene[©)]	ug/g creat.	5.38	5.36	5.25	5.5	12.9	10.7	3.6
OPP ortho-phenylphenol: fungicide and disinfectant	ug/g creat.	0.44	0.45	0.38	0.51	0.49	0.382	0.438

* NC = Not calculated. Proportion of results below limit of detection was too high to provide a valid result.
(a) metabolite of several pesticides including lindane and hexachlorobenzene **(b)** also found in tobacco smoke and certain polyaromatic hydrocarbons **©)** mothball ingredient.

References

1. Maibach HI, et al. 1971. Regional variation in cutaneous penetration in man. Arch Env Health 23:208-211.
2. Zwaveling JH, et al. 1987. Exposure of the skin to methyl bromide: a study of six cases occupationally exposed to high concentrations during fumigation. Hum Toxicol 6(6):491-495.
3. Jones K, et al. 2002. Factors affecting the extent of dermal absorption of solvent vapours: a human volunteer study. Ann Occ Hyg 47(2):145-150.
4. Davis JE, et al. 1983. Potential exposure of apple thinners to azinphosmethyl and comparison of two methods for assessment of hand exposure. Bull Env ContTox 31(6):631-638.
5. Abbott IM, et al 1987. Worker exposure to a herbicide applied with ground sprayers in the United Kingdom. Am Ind Hyg Assoc J 48(2):167–175.
6. Al-Jaghbir MT, et al. 1992. Dermal and inhalation exposure to dimethoate. Arch Env Contam Toxicol 22:358-361.
7. Aprea C, et al. 2001. Evaluation of respiratory and cutaneous doses and urinary excretion of alkylphosphates by workers in greenhouses treated with. Am Ind Hyg Assoc J 62(1):87-95.
8. Brouwer R, et al. 1993. Skin contamination, airborne concentrations, and urinary metabolite excretion of propoxur during harvesting of flowers in greenhouses. Am J Ind Med 24(5):593-603.
9. Brouwer DH, et al. 1992. Assessment of dermal and inhalation exposure to zineb/maneb in the cultivation of flower bulbs. Ann Occ Hyg 36(4):373-384.
10. Byers ME, et al. 1992. Exposure of a mixer-loader to insecticides applied to corn via a center-pivot irrigation system. Bull Env Contam Toxicol 49(1):58-65.
11. Fenske RA, et al. 1987. Occupational exposure to fosetyl-Al fungicide during spraying of ornamentals in greenhouses. Arch Env Contam Toxicol 16(5):615-621.
12. Leonard JA, et al. 1990. Exposure of workers using hand-held equipment during urban application of pesticides to trees and ornamental shrubs. Am Ind Hyg Assoc J 51(11):605-609.
13. Popendorf W, et al. 1995. Exposures while applying commercial disinfectants. Am Ind Hyg Assoc J 56(11):1111-1120.
14. Simpson GR, et al. 1972. Exposure to chlorinated hydrocarbon pesticides by pest control operators. Med J Australia 2:1060-1063.
15. Wojek GA, et al. 1981. Worker exposure to ethion in Florida citrus. Arch Env Contam Toxicol 10:725-735.
16. Fenske RA, et al. 1990. Worker exposure and protective clothing performance during manual seed treatment with lindane. Arch Env Contam Tox 19(2):190-196.
17. Spencer JR, et al. 1991. Chlorothalonil exposure of workers on mechanical tomato harvesters. Toxicol Lett 55(1):99-107.
18. Spencer JR, et al. 1995. Long vs. short monitoring intervals for peach harvesters exposed to foliar azinphos-methyl residues. Toxicol Lett 78(1):17-24.
19. Yoshida K, et al. 1990. Characteristics of applicator exposure to synthetic pyrethroid in ULV-handheld and ULV-ULA spray applications. J Env Sci Health B 25(2):151-167.
20.Wolf TM, Gallander KS, Downer RA, et a. 1999. Contribution of aerosols generated during mixing and loading of pesticides to operator inhalation exposure. Toxicol Lett 105(1):31-38.
21. Methner MM et al. 1996. Pesticide exposure during greenhouse applications. III. Variable exposure due to ventilation conditions and spray pressure. Appl Occ Env Hyg 11(3):174-180.
22. Methner MM, et al. 1994. Pesticide exposure during greenhouse applications. Part I: Dermal exposure reduction due to directional ventilation and worker training; Part II: Chemical permeation through protective clothing in contact with treated foliage. Appl Occ Env Hyg 9(8):567-574.
23. Fenske RA. 1988. Comparative assessment of protective clothing performance by measurement of dermal exposure during pesticide applications. Appl Ind Hyg 3(7):207-213.
24. Stewart P, et al. 1999. Exposure received from application of animal insecticides. Am Ind Hyg Assoc J 60(2):208-212.
25. Fenske RA. 1990. Minimizing dermal exposure to pesticides in greenhouses. NIOSH Grant No. K01-OH-00063.
26. Fenske RA. 1992. Minimizing Dermal Exposure to Pesticides in Greenhouses. Govt Reports Announcements & Index (GRA&I), Issue 05.
27. Coye MJ, et al. 1985. HHE Encinitas Floral Company, Encinitas, California.. NIOSH, U.S. DHHS, Cincinnati, Ohio, Report No. HETA-84-395-1588.
28.Coye MJ, Belanger PL. 1984. HHE, Amfac Garden Perry's, Carpenteria, California. NIOSH, U.S. DHHS, Cincinnati, Ohi, Report No. HETA-83-361-1463.
29. Alavanja MC, et al. 1999. Characteristics of persons who self-reported a high pesticide exposure event in the Agricultural Health Study. Env Res 80(2 Pt 1):180-186.
30. Alavanja MC, et al. 2001. Nested case-control analysis of high pesticide exposure events from the Agricultural Health Study. Am J Ind Med 39(6):557-563.
31. Keim SA, et al. 2001. Pesticide use by persons who reported a high pesticide exposure event in the agricultural health study. Env Res 85(3):256-259.
32. Chester G, et al. 1984. Occupational exposure and drift hazard during aerial application of paraquat to cotton. Arch Env Contam Toxicol 13(5):551-564.
33. DeCock J, et al. 1998. Exposure to captan in fruit growing. Am Ind Hyg Assoc J 59(3):158-165.
34. Methner MM, et al. 1994. Pesticide exposure during greenhouse applications, Part I. dermal exposure reduction due to directional ventilation and work training. Appl Occ Env Hygiene 9(8):560-566.
35. Carman GE, et al. 1982. Pesticide applicator exposure to insecticides during treatment of citrus trees with oscillating booms and air blast units. Arch Env Contam Tox 11:651-659.
36. Yates WE, et al. 1974. Closed system mixing and handling of pesticides in California. American Society of Agricultural Engineers Paper 74-1538, 11 pp.
37. Shandar A, et al. 1972. Exposure to chlorinated hydrocarbon pesticides by pest control operators. Med J Aust 2(19):1060-1063.
38. Cattani M, et al. 2001. Potential dermal and inhalation exposure to chlorpyrifos in Australian pesticide workers. Ann Occ Hyg 45(4):299-308.
39. Ames RG, et al. 1989. Health symptoms and occupational exposure to flea control products among California pet handlers. Am Ind Hyg Assoc J 50(9):466-472.
40. Curry P, et al. 1992. Comparison of exposure assessment guidelines for pesticides. Rev Env Contam Toxicol 129:79-93.
41. Blair A, et al. 2002. Reliability of reporting on life-style and agricultural factors by a sample of participants in the Agricultural Health Study from Iowa. Epidemiology 13(1):94-99.
42. Archibald BA, et al. 1995. Estimation of pesticide exposure to greenhouse applicators using video imaging and other assessment techniques. Am Ind Hyg Assoc J 56(3):226-235.
43. Fenske RA, et al. 1986. A Video imaging technique for assessing dermal exposure I. Instrument design and testing. Am Ind Hyg Assoc J 47(12):764-770.
44. Fenske RA, et al. 1986. A video imaging technique for assessing dermal exposure II. Fluorescent tracer testing. Am Ind Hyg Assoc J 47(12):771-775.
45. Fenske RA. 1988. Correlation of fluorescent tracer measurements of dermal exposure and urinary metabolite excretion during occupational exposure to malathion. Am Ind Hyg Assoc J 49(9):438-444
46. Fenske RA. 1993. Dermal exposure assessment techniques. Ann Occ Hyg 37(6):687-706.
47. Fenske RA, et al. 1997. Second generation video imaging technique for assessing dermal exposure (VITAE System) Am Ind Hygiene Ass J 58(9):636-645.
48. Archibald BA, et al. 1994. Fluorescent tracer and pesticide penetration through selected protective clothing. Bull Env Contam Toxicol 53(4):479-485.
49. Fenske RA, et al. 1991. Development of dermal and respiratory sampling procedures for human exposure to pesticides in indoor environments. J Expo Anal Env Epid 1(1):11-30.
50. Whitemore RW, et al. 1994. Non-occupational exposures to pesticides for residents of two U.S. cities. Arch Env Contam Toxicol 26(1):47-59.
51. Whyatt RM, et al. 2003. Contemporary-use pesticides in personal air samples during pregnancy and blood samples at delivery among urban minority

mothers and newborns. Env Health Persp 111:749-756.
52. Kamble ST, et al. 1992. Exposure of applicators and residents to chlordane and heptachlor when used for subterranean termite control. Arch Env Contam Tox 22:253-259.
53. Krieger RI, et al. 1996. Human disodium octaborate tetrahydrate exposure following carpet flea treatment is not associated with significant dermal absorption. J Expo Anal Env Epid 6(3):279-288.
54. Byrne SL, et al. 1998. Potential chlorpyrifos exposure to residents following standard crack and crevice treatment. Env Health Persp 106(11):725-731.
55. Griffin P, et al. 1999. Oral and dermal absorption of chlorpyrifos: A human volunteer study. Occ Env Med 56(1):10-13.
56. Black KG, et al. 1996. Dislodgeability of chlorpyrifos and fluorescent tracer residues on turf: comparison of wipe and foliar wash sampling techniques. Arch Env Contam Toxicol 31(4):563-570.
57. Cochran RC. 2002. Appraisal of risks from nonoccupational exposure to chlorpyrifos. Regul Toxicol Pharmacol 35(1):105-121.
58. Harris SA, et al. 2000. An evaluation of 24-hour urinary creatinine excretion for use in identification of incomplete urine collections and adjustment of absorbed dose of pesticides. Am Ind Hyg Assoc J 61(5):649–657.
59. Centers Disease Control. 2003. Second National Report on Human Exposure to Environmental Chemicals, NCEH Pub. No. 02-0716. January 2003. http://www.cdc.gov/exposurereport/
60. Omishakin MA. 1994. A survey of pesticides containers management among African-American agricultural workers in Mid-Delta of Mississippi, USA. J R Soc Health 114(2):81-82.
61. Owens JM, Guiney PD, Howard PH, et al. 2000. Indoor household pesticides: hazardous waste concern or not? Rev Env Contam Toxicol 164:27-68.
62. Csiszar E, et al. 1998. Reduction in human exposure to pesticide using traditional work clothing fabrics with chemical finishing: carboxymethylation and starch. Arch Env Contam Toxicol 35(1):129-134.
63. Easley CB, et al. 1982. Methyl parathion removal from denim fabrics by selected laundry procedures. Bull Env Contam Toxicol 27(1):101-108.
64. Finley EL, et al. 1979. Reduction of methyl parathion residues on clothing by delayed field re-entry and laundering. Bull Env ContamToxicol 22(4/5):590,598. [Publ. error: title pg 590, article pge 598].
65. Davies JE, et al. 1982. Reduction of pesticide exposure with protective clothing for applicators and mixers. J Occ Med 24:464-468.
66. Braun HE, et al. 1990. Removal of organophosphorus, organochlorine and synthetic pyrethroid insecticides and organochlorine fungicides from coverall fabric by laundering. Bull Env Contam Toxicol 44(1):92-99.
67. Finley EL, et al. 1974. Efficacy of home laundering in removal of DDT, methyl parathion, and toxaphene residues from contaminated fabrics. Bull Env Contam Tox 12:268-274.
68. Easley CB, et al. 1983. Laundering procedures for removal of 2,4-dichlorophenoxyacetic acid ester and amine herbicides from contaminated fabrics. Arch Env ContamToxicol 12(1):71-76.
69. Gladen BC, et al. 1998. Exposure opportunities of families of farmer pesticide applicators. Am J Ind Med 34(6):581-587.
70. Easter EP, et al. 1985. The efficacy of laundering captan and Guthion contaminated fabrics. Arch Env Contam Tox 14:281-287.
71. Hild DN, et al. 1989. Laundry parameters as factors in lowering methyl parathion residue in cotton/polyester fabrics. Arch Env Contam Toxicol 18(6):908-914.
72. Clifford NJ, et al. 1989. Organophosphate poisoning from wearing a laundered uniform previously contaminated with parathion. JAMA 262(21):3035-3036.
73. Chiao-Cheng J, et al. 1988. Carbamate insecticide removal in laundering from cotton and polyester fabrics. Arch Env Contam Tox 17:87-94.
74. Chester G, et al. 1987. Worker exposure to, and absorption of cypermethrin during serial application of an "ultra low volume" formulation to cotton. Arch Env Contam Tox 16:69-78.
75. Castro Cano ML, et al. 2001. Gas chromatographic method for assessing the dermal exposure of greenhouse applicators to dimethoate and malathion. J Chromatogr Sci 39(8):345-350.
76. Knaak JB, et al. 1989. Mixer-loader-applicator exposure and percutaneous absorption studies involving EPTC herbicide. Safety related to exposure. In: Wang RGM et al. (Eds), Biological Monitoring for Pesticide Exposure pp 2880-303. ACS Symposium Series 382, Washington DC.
77. Knaak JB, et al. 1986. Estimating the hazard to humans applying nemacur 3EC with rat dermal-dose Che response data. Bull Env Contam Toxicol 37(2):159-163.
78. Canossa E, et al. 1993. [Dosage indicators in farm workers exposed to mancozeb]. Medicine del Lavoro 84(1):42-50.
79. Woodruff TJ, et al. 1994. Evaluating health risks from occupational exposure to pesticides and the regulatory response. Env Health Persp 102:1088-1096.
80. Davies JE. 1972. Effects of different kinds of exposures on man as determined through laboratory testing. In: Proceed. Nat. Conf. Protective Clothing and Safety Equipment for Pesticide Workers, Washington DC, pp 151-154
81. Rutz R, et al.1992. Exposure to pesticide mixer/loaders and applicators in California. Rev Env Contam Toxicol 129:121-139.
82. 0Fenske RA. 1988. Visual scoring system for fluorescent tracer evaluation of dermal exposure to pesticides. Bull Env Contam Toxicol 41(5):727-736.
83. Fenske RA. 1990. Nonuniform dermal deposition patterns during occupational exposure to pesticides. Arch Env Contam Toxicol 19(3):332-337.
84. Coffman CW, et al. 1999. Pesticide deposition on coveralls during vineyard applications. Arch Env Contam Toxicol 37(2):273-279.
85. Krieger RI, et al. 2000. Captan fungicide exposures of strawberry harvesters using THPI as a urinary biomarker. Arch Env Contam Toxicol 38(3):398-403.
86. Zweig G, et al. 1983. Simultaneous dermal exposure to captan and benomyl by strawberry harvesters . J Agric Food Chem 31(5):1109-1113.
87. Duncan RC, et al. 1985. Monitoring study of urinary metabolites and selected symptomatology among Florida citrus workers. J Toxicol Env Health 16:509-521.
88. Melnyk LJ, et al. 1997. Dietary exposure from pesticide application on farms in the Agricultural Health Pilot Study. J Expo Anal Env Epid 7(1):61-80.
89. Nemec SJ, et al. 1968. Methyl parathion adsorbed on the skin and blood cholinesterase levels of persons checking cotton treated with ultra-low-volume sprays. J Econ Entomol 61(6):1740-1742.
90. Hernandez-Valero MA, et al. 2001. Evaluation of Mexican American migrant farm worker work practices and organochlorine pesticide metabolites. Am J Ind Med 40(5):554-560.
91. Fenske RA, et al. 1999. Comparison of three methods for assessment of hand exposure to azinphos-methyl (Guthion) during apple thinning. Appl Occ Env Hyg 14(9):618-623.
92. Aprea C, et al. 1999. Multiroute exposure assessment and excretion of urinary metabolites of fenitrothion during manual operations on treated ornamental plants in greenhouses. Arch Env Contam Toxicol 36(4):490-497.
93. Lavy TL, et al. 1992. Conifer seedling nursery worker exposure to glyphosate. Arch Env Contam Tox 22:6-13.
94. Machera K, et al. 2003. Determination of potential dermal and inhalation operator exposure to malathion in greenhouses with the whole body dosimetry method. Ann Occ Hyg 47(1):61-70.
95. Brouwer DH, et al. 1992. Pesticides in the cultivation of carnations in greenhouses: part I - exposure and concomitant health risk. Am Ind Hyg Ass J 53:575-587.
96. Brouwer R, et al. 1992. Risk assessment of dermal exposure of greenhouse workers to pesticides after re-entry. Arch Envir Contam Toxicol 23:273-280.
97. Lavy TL, et al. 1993. Measurements of year-long exposure to tree nursery workers using multiple pesticides. Arch Env Contam Tox 24:123-144.
98. Asakawa F, et al. 1989. [The actual state of occupational exposure to chlorpyrifos of termite control workers]. Nippon Eiseigaku Zasshi 44(4):921-928.
99. Garrod AN, et al. 1998. Occupational exposure through spraying remedial pesticides. Ann Occup Hyg 42(3):159-165.

100. Edmundson WF, et al. 1972. p,p'-DDT and p,p'-DDE in blood samples of occupationally exposed workers. In: Davies JE, et al (eds) Epidemiology of DDT, Futura Pub.Co. Inc., Mount Kisco, New York, pp 57-65.
101. Slocum AC, et al. 1991. Spray deposition patterns during simulated work activities by lawn care specialists. J Env Sci Health B 26(3):259-278.
102. Fenske RA, et al. 1990. Multi-route exposure assessment and biological monitoring of urban pesticide applicators during structural control treatments with chlorpyrifos. Toxicol Ind Health 6(3-4):349-371.
103. Griffin P, et al. 2000. The in vitro percutaneous penetration of chlorpyrifos. Hum Exp Toxicol 19(2):104-107.
104. Smallwood AW, et al. 1992. N,N'-diethyl-m-toluamide (m-DET): analysis of an insect repellent in human urine and serum by high-performance liquid chromatography. J Anal Toxicol 16(1):10-13.
105. Bristol DW, et al. 1982. Chemical analysis of human blood for assessment of environmental exposure to semivolatile organochlorine chemical contaminants. J Anal Toxicol 6(6):269-275.
106. Cline RE, et al. 1989. Pentachlorophenol measurements in body fluids of people in log homes and workplaces. Arch Env Contam Tox 18:475-481.
107. Bukowski JA, et al. 1995. Simulated air levels of volatile organic compounds following different methods of indoor insecticide application. Env Sci Technol 29(3):673-676.

Chapter 3
Acute Pesticide-Related Illness

Introduction
Acute effects are those that occur close in time to exposure, within a few minutes, a few hours, at the most a few days. The most important factor in pesticide toxicity is the amount it takes to poison, kill or do harm.

The EPA classifies all pesticides into one of four acute toxicity categories. Category I defines the most toxic, and Category IV the least toxic. The classification is based on how much of the chemical it takes to kill fifty percent of laboratory animals by feeding it to them, putting it on the skin, or inhaling it, called the oral, dermal, or inhalation LD_{50} (ell dee fifty).

Acute Health Effects of Pesticides

Irritation of the eyes, nose, and throat
Dermatitis
Systemic Poisoning
Death

The lower the LD_{50} the less of the pesticide it takes to poison the animals, and therefore the more toxic it is. For example, the oral LD_{50} of parathion is 4 m/kg and of malathion 1,000 mg/kg. This means that parathion is 250 times more toxic than malathion (or malathion is 250 times less toxic than parathion); that it would take 250 times more malathion to kill the animals than parathion (or 250 times less than parathion). See Appendix D for EPA classification criteria.

Acute Health Effects
Acute health effects range from burning, stinging and tearing of the eyes, to skin rashes, to serious poisoning and death. The best single source of information on acute pesticide poisoning is the fifth edition of the EPA's "Recognition and Management of Pesticide Poisoning", which is also available online[1].

Organophosphate (OP) insecticide toxicity is the leading cause of major morbidity and death in the insecticides class. The clinical syndrome of OP toxicity varies widely, ranging from the classic cholinergic syndrome to flaccid paralysis and intractable seizures. The mainstays of therapy for OP-poisoned patients are atropine, pralidoxime, and benzodiazepines. Tachycardia is not a contraindication to treatment with atropine in OP toxicity. Atropine should be administered to alleviate respiratory distress, symptomatic bradycardia, and as an adjunct to benzodiazepines to alleviate seizure activity. Atropine should not be administered systemically to alleviate miosis. In acute OP toxicity, a continuous pralidoxime infusion should be considered. Intermediate syndrome and OP-induced delayed neuropathy may occur in select patients with OP poisoning.

Irritant effects: The most common acute effect of pesticides is irritation of the eyes, nose, and throat. Of the 667 cases of pesticide related illness reported to the California Environmental Protection Agency in 2001, 21.6% were eye irritant effects, 11.1% to the skin[2]. The resulting tearing, stinging, burning, scratchiness and itching, can be from the active ingredient pesticide, an inert ingredient, or a combination[3,4,5,6].

Sulfur, a frequent source of eye and nose irritation, is essentially unreported by farm workers since it is so common. A study of apricot sulfurization found eye and nose irritation in 70% of the workers[7]. Eye irritation is on a frequently reported symptom in drift-related community exposures, including paraquat[8], metam sodium[9],[10] methyl isocyanate[11,12,13], and Mocap[14], methyl bromide and chloropicrin[15].

Effects on the Eye: Pesticides can cause chemical conjunctivitis that looks like pink eye. If pesticides splash directly into the eyes they can cause corneal abrasions or ulcers, damaging the layers of the cornea. With complete removal of the pesticide from the eye and proper treatment, the cornea should heal completely. If the pesticide or inert ingredient is corrosive and not thoroughly removed, permanent scarring can lead to blindness. Eyes symptoms often persist for some time after recovery from acute pesticide poisoning[16,17].

Transient ocular symptoms occurred in 70%, and temporary injury in 2% of 1,513 glyphosate (Roundup) related calls to a poison control center in the U.S. One injury took more than two weeks to resolve[18]. Topical irritation of the eyes was found in 49% of 815 glyphosate (Roundup) related reports from 1982-1997 to the pesticide surveillance

program of Cal-EPA[19]. Three outbreaks of conjunctivitis occurred in 35 workers in a California nut-packing facility from 1987 to 1988 . Phosphine gas was suspected, but ammonia gas, aluminum hydroxide dust, almond hulling dust, or propargite (Omite 6-E) could also have been responsible, or contributory[20]. Exposure-related conjunctivitis was found in 7% of agricultural pesticide applicators in Ecuador[21].

Paraquat, an epithelial toxin, is a frequent cause of eye lesions in agricultural workers[22], and can cause severe ocular damage from splashes, spills, and other occupational exposures[23,24,25,26].

Pesticide applicators in the Agricultural Health Study (AHS)[a] who reported retinal degeneration had a significant 180% increase in risk related to fungicide use. The risk increased with cumulative days of exposure and use of methods involving greater personal exposure . Organochlorine and carbamate insecticides were also related but the associations were less consistent [27].

Macular defects were found in pesticide applicators in India [28]. Optic neuritis associated with organophosphate exposure was found in several studies[29,30,31,32,33]. Opsoclonus (ocular bobbing) occurred in organophosphate poisoning[34,35,36,37] and in chlordecone (Kepone) poisoning[38]. Optic atrophy is rare and the cases reported were from methyl bromide exposure[39,40].

Cataracts have been related to ethylene oxide exposure[41,42,43], and methyl isocyanate in the Bhopal, India incident[13]. Organophosphate exposed farmers were found to have increased cortical wedging but no increase in cataracts[44].

Label Warning Statements that Indicate a Pesticide May Cause Allergic Dermatitis

This product is a skin sensitizer.

May cause skin reaction in rare cases.

May cause contact sensitization following repeated contact with skin of susceptible individuals. If sensitization reactions result, contact a physician

Frequent or repeated exposure to this product may cause allergic reactions in some people.

Reports from Japan of adverse ocular effects from organophosphate exposure, including myopia in adults and children have not been found in other countries[45,46,47].

A study of two organophosphate poisoned patients found that PET scanning (positron emission tomography) can confirm severe cortical visual loss even when standard eye exams and MRI (magnetic resonance imaging) examinations are normal[48].

Skin Effects

Pesticides can cause both irritant and allergic contact dermatitis; most are the irritant type. The immunologically based allergic response (sensitization) can be disabling or life threatening,. Pesticide manufacturers are required to put a warning on the label of commercial and over-the-counter products if the active ingredient is a skin sensitizer. Figure 2 shows some of these statements for some over-the-counter products.

Pesticide Associated Contact dermatitis

Most pesticide related dermatitis is the irritant type, and not an immunological sensitization or allergic reaction. Most reports of allergic contact dermatitis are anecdotal case reports, but some studies using patch testing have been done. More cases have been reported from fungicide exposure than other classes of pesticides (see Table 1).

There is an excellent review and discussion of skin reactions to pesticides[49]

Skin Reactions to Deet (Off): N,N-diethy-m-toluamide (deet, Off) is an insect repellent designed for use on human skin. A severe anaphylactic reaction occurred in a 42 year old woman with no prior history of allergy, who touched a companion who had just applied 52% deet. Rapid generalized pruritus progressed to angioedema, nausea, hypotension, and unconciousness[117]. Military personnel in south Vietnam who applied 50% deet, developed a burning sensation, erythema (redness), blisters, and a bullous eruption in the antecubital fossea which led to ulceration and scarring in some cases[50, 51]. Skin rash has been reported after topical application[52,53,54], and a

[a] A cohort study of licensed pesticide farmer applicators in Iowa and North Carolina begun in 1994, conducted by the National Cancer Institute Occupational Epidemiology Branch.

vesicobullous reaction from occupational exposure[55,56]. Applications of one to two milliliters of a 50% concentration for five days to the skin of volunteers produced paresthesia, blisters and local skin effects[57].

Table 1
Pesticides Related to Allergic Contact Dermatitis

Antimicrobials	Fentichlor[82,83]	Chloridazon[106]	d-Limonene[115, 116, 117]
Benzalkonium chloride[58,59]	Fluazinam[84]	Chlorpropham[54]	Methiocarb[118]
Chloramine[60]	Imazalil[71]	Dalapon[84]	Methomyl [119,120]
Fumigants	Maneb,Mancozeb[85,86,87,88,89,90,91,92,93]	Norflurazon[107]	Parathion[74]
Dazomet[61]	PCNB[94]	Paraquat [77,108]	Pyrethrum[121,122]
Ethylene oxide[62]	Propineb[95]	Phenmedipham[109]	**Inerts**
1,3-Dichloropropene[63,64, 65]	Thiabendazole[71,96]	Propachlor[110,111]	Ethylenediamine[123,124,125]
Fungicides	Thiram[97]	Trifluralin[96,99]	**Repellents**
Anilazine (Dyrene)[66]	Triforine[98]	**Insecticides**	Deet (Off [126,127]
Benomyl[67,68]	Zineb [82,84,99,100,101]	Barban[112]	
Captafol[69,70,71,72,73]	**Herbicides**	Dichlorvos[68,90]	
Captan[60,62,63,74,75]	Alachlor[102,103]	Dimethoate[113]	
Chlorothalonil[76,77,78,79,80,81]	Allidichlor[104]	Fenvalerate [114]	
Folpet [60,62,63]	Benefin[105]		

Other Skin Conditions (Table 2)

Pesticide exposure is linked to other skin disorders, including chloracne[128,129,130,131,132,133] ; dysesthesias[134,135,136,137,138]; pemphigus [139,140,141,142,143]; hypopigmentation[144,145,146,147]; vitiligo [148,149,150], ashy dermatitis[151]; nail damage (onchopathy)[152,153,154,155,156,157], and one report of localized scleroderma[158].

Omite-CR Reentry Poisoning

It is rare for a pesticide to cause skin poisoning of entire crews of farm workers, as occurred in California in 1986. Over a two week period, 114 of 198 orange pickers developed redness, itching, and chemical burns of the skin, resulting in small papules and vesicles (blisters), weeping, crusting, peeling, and hyperpigmentation[5,159].

It is also rare for an inert ingredient to be implicated in such a large outbreak. The cause of the episode was a reformulation of the widely used miticide propargite (Omite). The inert ingredient polyvinyl acetate was added to the new formulation, called Omite-CR, to prevent citrus leaf burn by delaying degradation on the leaves. That this would also prolong the length of time the pesticides stayed on the skin of the workers picked oranges sprayed with the new formulation was not considered.

The reentry interval (amount of time legally required after application of a pesticide before workers are allowed to reenter the treated field for cultivation or harvest activities) for propargite/Omite at the time of the poisoning was seven days. An emergency extension by Cal-EPA increased the reentry interval to 10 days, and then again to 14 days. Based on residue degradation studies of the Omite-CR, a final reentry interval of 42 days was enacted[160]. Omite-CR is no longer registered for use in California.

Table 2
Other Pesticide-Related Skin Conditions

Chloracne	
Methazole[a]	Manufacture contaminant
Pentachlorophenol	Manufacture, treated wood
Propanil	Manufacture
2,4,5-T[b]	Lawn sprayer, farm worker
Dysaesthesias	
λ-Cyhalothrin	Malaria wrkrs
Fenvalerate	Agric. applicator
Pyrethroids	Human study
Pemphigus	
DDT	Gardener
Diazinon	Sun exposure
Dichloropropene	Farmer
Pentachlorophenol	Non-occupational
Pigmentation Changes	
Alachlor (Lasso)	Hypopigmentation
Barban	Depigmentation[(c)]
Chlorothalonil	Ashy dermatitis[(d)]
Dinitrophenol	Vitiligo occupational
Dichloropropene[(36)]	Hypopigmentation
Mancozeb	Vitiligo
Methyl bromide	Hyperpigmentation
Paraquat	Hypopigmentation farmer[(e)]
Onchopathy (nail damage)	
DNOC	Agriculture
Mancozeb	Occupational
Paraquat	Reported with all sources of work exposure
Scleroderma (**Localized**)	
2,4,5-T	Lawn sprayer

(a) From contaminant 3,3',4,4'- tetrachloroazo-benzene **(b)** Also exposed to 2,4-D, bromofenoxin and picloram. **[c]** Partial repigmentation 6 wks later **(d)** Erythema dyschromicum persistans. In 70% lesions in sun exposed areas .**(e)** In black cocoa plantation workers.

Pesticide Poisoning: Organophosphates

Systemic poisoning occurs when pesticide enter the blood stream and spread throughout the body. The pesticides responsible for more occupational, accidental, and suicidal poisonings and deaths in the U.S. and throughout the world than any other, are the organophosphate insecticides. Similar to nerve gas, but less potent, they exert their toxic effect by interfering with a critical chemical in the nervous system called acetylcholine (ASS uh teel COAL een), which is essential for the transmission of nerve impulses. After acetylcholine is used to transmit nerve impulses across gaps (synapses) between nerve cells and receptors on muscles, glands, and other sites throughout the bod, it is no longer needed and must be deactivated until needed again.

Organophosphate Pesticides
Common Name (Brand Name)

Acephate (Orthene)	Isofenphos (Oftanol)
Azinphosmethyl (Guthion)	Malathion
Chlorpyrifos (Dursban, Lorsban)	Merphos (Folex)
DEF (tribufos)	Methamidophos (Monitor)
Demeton (Systox)	Methidathion
Diazinon	Methyl parathion
Dichlorvos/DDVP (Vapona)	Mevinphos (Phosdrin)
Dimethoate (Cygon)	Monocrotophos (Azodrin)
Disulfuton (Disyston)	Naled (Dibrom)
Ethion	Parathion (ethyl)
Ethoprop (Mocap)	Phorate (Thimet)
Fenamiphos (Nemacur)	Phosmet (Imidan)
Fensulfothion (Dasanit)	Terbuphos (Counter)
Fenthion	Tetrachlorvinphos (Gardona
Fonofos (Dyfonate)	

The enzyme responsible for deactivating acetylcholine is cholinesterase[b] (coal in ESTER ase). The organophosphate and N-methyl carbamate insecticides poison by binding (locking on) to cholinesterase and inhibiting its activity in the brain and peripheral nervous system. This allows acetylcholine to pile up at nerve junctions causing the signs and symptoms of poisoning.

Cholinesterase Activity

There are two type of cholinesterase affected by pesticides. Plasma or serum cholinesterase (pseudo-cholinesterase) is made in the liver. "True" cholinesterase is found in red blood cells (RBC).

In general plasma cholinesterase activity decreases more rapidly and regenerates more quickly, usually within a week to ten days after overexposure to organophosphates or N-methyl carbamates have lowered the activity level. After mild poisoning, sometimes a rebound effect occurs resulting in elevated levels. Plasma cholinesterase can be affected by liver disease, anemia, and other illnesses, and is not as reliable an indicator as RBC cholinesterase.

Label Statements Indicating a Product Contains an Organophosphate Insecticide

Atropine is an antidote

This product contains a cholinesterase inhibiting pesticide.

RBC cholinesterase activity decreases less rapidly and regenerates more slowly. It is more reflective of functional cholinesterase in the brain and nervous system and is biochemically the same enzyme. RBC cholinesterase regenerates at about 1% per day; therefore a 30% reduction in activity would take about a month to return to pre-exposure baseline levels. RBC cholinesterase has no known function and it is not known why how or why it cam to be present.

Potential chronic sequelae related to decreases in cholinesterase activity is discussed in Chapter 7.

California's Cholinesterase Monitoring Regulations

The State of California has required cholinesterase monitoring under medical supervision for workers who "regularly handle" Toxicity Categories I and II organophosphates or N-methyl carbamates since 1974[161]. "Regularly handle" means handling pesticides during any part of the day for more than six calendar days in any 30 day qualifying period beginning on the first day of handling.

The employer is required to arrange with a physician to obtain baselines pre-exposure plasma and RBC cholinesterase activity levels and interpret the results. This baseline value must be the average of two or more tests taken at least 72 hours but not more than 14 days apart at the same laboratory. One test is permissible under the regulations if two cannot be obtained. If two tests are done and the difference between them exceeds 15 percent, a

[b] Acetycholinesterase is commonly referred to as cholinesterase, and often abbreviated as AChe or Che.

third baseline test must be performed. The average of the two closest values should be considered the true value. Baselines must be measured before exposure begins and repeated at a minimum of every two years.

If plasma or RBC cholinesterase or RBC levels drops to 80% of baseline , that is a 20% reduction in activity, an investigation of work practices is required, including safety equipment use and condition, sanitation, and pesticide handling procedures

If plasma cholinesterase levels drops to 60% or less of baseline, that is a 40% reduction in activity, or RBC cholinesterase drops to 70% , a 30% reduction in activity from baseline, the employee must be removed from exposure, and may not be returned until cholinesterase activity reaches80% or more of their respective baseline values.The employer must maintain written records of any investigations, results, and recommendations, and the dates of removal and return to exposure; all values and reports must be available to the employee, and kept for a minimum of three years. See Appendix E for a summary of cholinesterase testing and how and when to do the test.

Table 3
Signs and Symptoms of Poisoning by Cholinesterase InIhibiting Pesticides
(Organophosphates, N–methyl Carbamates)

Mild Poisoning	
Headache	Blurry vision
Dizziness	Excess sweating
Fatigue	Salivation (drooling)
Nausea	Muscle pain, cramping
Vomiting	Abdominal pain
Chest pain	Diarrhea
Moderate Poisoning	
Severe weakness	Confusion
Difficulty walking	Difficulty concentrating
Difficulty talking	Small pupils (miosis)
Muscle twitching	
Severe Poisoning	
Loss of consciousness	Cyanosis (turns blue)
Marked miosis	Convulsions
Difficulty breathing	Coma
Involuntary urination	Death
Involuntary defecation	

Oxon Formation
Organophosphate insecticides that contain sulfur in a thion group (P=S) must undergo transformation in the liver before they can inhibit cholinesterase. Oxygen is substituted for the sulfur in the thion group to form an oxon (P=O), e.g. paraoxon from parathion, maloxon, from malathion, chlorpyrifos oxon from chlorpyrifos, and so on. Organophosphates without this thion group, such as mevinphos (Phosdrin) are direct inhibitors of cholinesterase.

The oxon is more toxic than the parent pesticide and is the actual cholinesterase inhibitor. The enzyme responsible for this conversion is called paraoxonase. Paraoxonase activity levels are genetically determined, and an individual's genotype and phenotype can affect their susceptibility to poisoning. Five polymorphisms are known to contribute to a 15-fold differences in plasma paraoxon levels among individuals. Newborn baby's levels are four times lower level than adult levels, which are reached around one year of age[162].

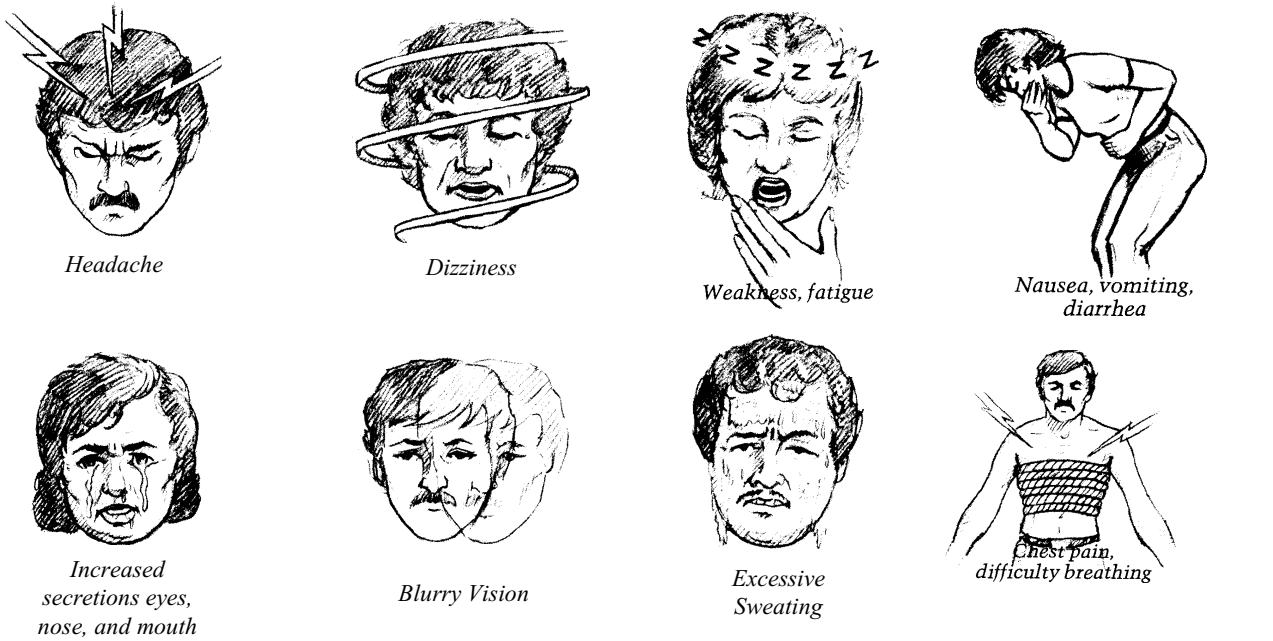
People with lower levels of paraoxonase may be less susceptible to poisoning since the oxon conversion will be slower. Those with higher levels may be more susceptible since the oxon conversion will be faster[163,164]. A worker in California poisoned by dialiflor (Torak), was found to have exposure to unexpectedly large amounts of dialifor oxon, which is twenty times more efficient in inhibiting cholinesterase than the parent chemical. Dialaflor is quite persistent compared to other organophosphate insecticides[165].

Animal studies have investigated whether gene therapy could prevent organophosphate poisoning[166]. Since paraoxonase is an HDL-associated enzyme, its role in cardiovascular diseases is an area of study[167], and as an "antioxidant" protein in certain neurodegenerative diseases including Parkinson's[168].

Signs and Symptoms of Poisoning (Table 3, Figure 1)
Poisoning by organophosphates and N-methyl carbamates (see discussion of N-methyl carbamate poisoning below) results in cholinergic effects at nerve junctions (muscarinic effects), at skeletal muscle (nicotinic effects), and in the brain. Death is usually from respiratory failure due to fluid in the lungs (pulmonary edema).

Atropine, the antidote for organophosphate poisoning, blocks the effects of acetylcholine, and must be given in much higher does than for other medical indications. Tolerance to high doses of atropine can be diagnostic of organophosphate poisoning. The oxime protopam (2-PAM) is another antidote which can reverse cholinesterase inhibition, but must be administered within 24 hours of poisoning.

Figure 1. Signs and Symptoms of Organophosphate and N-methyl Carbamate Insecticide Poisoning



Vincent Perez / Artist

Intermediate Syndrome

The intermediate syndrome appears one to four days after proper treatment and apparent improvement of organophosphate poisoning, and can last for several days or weeks. Prolonged cholinesterase inhibition results in respiratory paralysis, cranial motor nerve palsies, proximal limb muscle and neck flexor weakness, and depressed tendon reflexes. The condition is rare and relates to the to the severity of poisoning and not to the specific pesticide involved. Most cases are in severely poisoned patients who attempt suicide. Many countries have reported cases, including Belgium[169,170, 171,172], Canada[173], China[174,175], France[176], Germany[177], India [178,179,180,181,182,] Morocco[183], Poland [184,] South Africa [185], Sri Lanka[186,187,188], Turkey[189], Arkansas[190], the U.S.[191] , and Venezuela[192]. The pesticides involved were chlorpyrifos, dimethoate, fenitrothion, malathion, metasystox, methyl parathion, monocrotophos, omethoate, and parathion.

Farm Worker Crew Poisonings (Table 4)

Ever since the introduction of organophosphates in1943, farm workers have been at risk from toxic pesticide residues on the crops they cultivate and harvest. These dislodged foliar residues (DFR) are responsible for unknown thousands of poisonings. See Table 4 for reported incidents in California.

Cauliflower workers: mevinphos and phosphamidon

Sixteen farm workers in Monterey County, California were poisoned by mevinphos (phosdrin) and phosphamidon when they were sent into a cauliflower field that had been sprayed six hours earlier. State regulations required a 72 hour interval. Signs and symptoms of poisoning included blurred vision, dizziness, weakness, disorientation, headache, nausea, vomiting, and cramping. Plasma Che activity was inhibited by about 66% in eight workers receiving medical and red blood cell (RBC) activity by 33%. Eleven days after exposure, plasma and RBC cholinesterase were still decreased 34% and 39% respectively.

It took 57 days for plasma activity to return to 95% of normal, and 66 days for RBC. An important finding was that

symptoms of poisoning were more highly correlated with the rapidity of cholinesterase decline rather than the amount of reduction in activity[193].

Lettuce workers: mevinphos
Thirty-one of 44 farm workers and three agricultural officials were poisoned in Monterey, California after entering a field of iceberg lettuce that had been sprayed earlier that day with mevinphos. Signs and symptoms included dizziness, visual disturbances, headache, and nausea. Two workers were hospitalized; two had abnormal plasma ChE activity. Several workers were unable to return to work the next day because of continuing symptoms. ChE and AChE values increased significantly over the next 2 weeks. A retrospective evaluation based on the followup measurements indicated that during the acute stage of the incident plasma ChE and erythrocyte AChE had been decreased by a mean of 15.6 and 5.6%, respectively[194].

Grape pickers: dialifor and phosphalone
One of the first reported organophosphate crew poisoning of farm workers occurred in Madera, California in 1976, when 108 of 120 grape pickers became ill from exposure to dialifor (Torak) and phosphalone (Zolone). Eighty-five required medical attention and four were hospitalized. The average plasma and red cell cholinesterase activity was decreased by 60%. Workers had been sent into the vineyards before the required 30 day waiting period. Subsequent investigation found workers were exposed to foliage containing up to 57 ppm phosalone and up to 2.3 ppm of phosalone oxon. The estimated concentration of dialiflor in the fields was 100 ppm, a highly significant exposure level.

The growers' records of application date and amounts applied contained no indication that these residues could have been possible at the time of harvesting. A criminal complaint was filed against the grower, who was fined $1,750 for violations including the use of Torak without a valid permit and not maintaining record of use. The grower also paid substantial medical expenses, and lost heavily from grapes placed under quarantine A physician was also fined in this action for failure to report occupational injury to the Division of Labor Statistics and Research[195,196].

Grape pickers: phosalone
Thirty members of a crew of farm workers in Madera County, California became ill with weakness, dizziness, and gastrointestinal symptoms nine days after they began picking grapes. Ten were admitted to the hospital, and four had episodes of severe sinus bradycardia (slow heart rate) persisting for several days. Two workers developed a transient atrioventricular dissociation (abnormal heart rhythm) at the time of admission. Of 20 workers tested, all had moderate to severe inhibition of both plasma and RBC cholinesterase. Phosalone had been last applied to the vineyard 29 days earlier[197].

Apple orchard workers: mevinphos. An outbreak of mevinphos (Phosdrin) poisoning in 27 workers in 19 different apple orchards in Washington State occurred in the summer of 1993. Most cases (83%) were in airblast sprayer crews overexposed during mixing, loading, or application operations. The remaining cases were due to indirect contact, such as reentering recently treated orchards. All workers exposed during mixing, loading, or application sought treatment in emergency rooms. Seven required hospitalization, four in intensive care. Fourteen of 16 cases tested had cholinesterase depressions of 25% or more, and more than a 50% reduction. I

Subsequent investigations revealed failure to observe labeling requirements for protective equipment, lack of proper supervision, deficient hazard communication and training, and poor respirator maintenance. These incidents eventually led to suspension of mevinphos for use on apples and other tree fruits[198].

Emergency personnel. Three emergency room personnel were poisoned and required treatment after exposure to a contaminated patient[199]. Two emergency medicine personnel required hospitalization and treatment for organophosphate poisoning after giving mouth to mouth resuscitation to a suicide victim who later died[200].

Table 4
Reported Crop Residue Incidents of Group Poisonings from Re-entry or Drift
California - 1949 to 2000

Year	County	Number Ill	Crop	Pesticide(s)
1949	Yuba	10-25	Pears	Parathion
1951	Kern	16	Grapes	Parathion
1952	Riverside	1	Oranges	Parathion
1953	Riverside	7	Oranges	Parathion
1953	Riverside	-	Citrus	Parathion
1953	San Bernardino	-	Citrus	Parathion
1959	Various	275	Citrus	Parathion
1961	Tulare	10	Lemons	Parathion
1963	Stanislaus	94	Peaches	Parathion
1966	Tulare	18	Oranges	Parathion
1966	Los Angeles	11	Oranges	Parathion, Malathion
1966	Tulare	9	Oranges	Parathion, Ethion
1967	Stanislaus	24	Peaches	Guthion, Ethion
1967	Merced	3	Peaches	Guthion
1968	Tulare	19	Oranges	Parathion
1970	Tulare	3	Lemons	Dioxathion, Naled
1970	Tulare	2	Oranges	Parathion, Ethion
1970	Tulare	8-11	Oranges	Guthion, Ethion
1970	Kern	35	Oranges	Parathion
1970	Tulare	11	Oranges	Parathion, Malathion
1971	Fresno	8	Olives	Parathion
1972	Fresno	3	Oranges	Parathion
1972	Tulare	9	Oranges	Parathion
1972	Monterey	31	Lettuce	Parathion
1973	Fresno	27	Grapes	Phosalone, Dialifor
1974	Fresno	2	Grapes	Phosalone, Guthion
1975	Tulare	16	Oranges	Parathion
1976	Madera	118	Grapes	Phosalone, Dialifor
1977	Fresno	25	Oranges	Parathion
1978	Tulare	7	Grapes	Ethion
1980	Merced	6	Peaches	Guthion
1980	Monterey	22	Cauliflower	Phosdrin, Phosphamidon
1981	Monterey	41	Lettuce	Phosdrin
1982	Tulare	17	Oranges	Parathion
1982	Monterey	35	Cauliflower	Phosdrin, Metasystox-r
1983	Monterey	23	Cauliflower	Metasystox-r,dimethoate
1986	Tulare	121	Oranges	Propargite (Omite-cr)
1987	Fresno	35	Peaches	Guthion
1987	Madera	54	Grapes	Phosalone
1987	Fresno	24	Grapes	Phosalone
1993	All Counties	117	All Crops	Mixed
1994	All Counties	109	All Crops	Mixed
1997	Colusa	10	Rice	Methyl Bromide
1997	Imperial	10	Melons	Methomyl, Esfenvalerate,endosulfan
1997	Imperial	16	Melons	Benomyl, Triadimefon
1997	Riverside	31	Alfalfa	Inert Ingredient (Adjuvant)
1997	Tulare	12	Oranges	Not Listed
1997	Tulare	14	Grapes	Mixed
1998	Fresno	34	Cotton	Carbofuran
1998	Merced	12	Nectarines	Chlorpyrifos, Copper Sulfate
1998	Monterey	12	Apples	Diazinon, Fenarimol
1999	Fresno	13	Cotton	Chlorpyrifos, Naled
1999	Madera	10	Grapes	Chlorpyrifos, Lime-sulfur
1999	Tulare	171	Soil	Metam-sodium
2000	Kings	58	Eggs	Dimethoate
2000	Tulare	26	Almonds	Propargite, Chlorpyrifos
2000	Ventura	28	Lemons	Chlorpyrifos

N–Methyl Carbamates

N-methyl carbamates are cholinesterase inhibitors and share a common mechanism of action with the organophosphates. Unlike the organophosphates, the inhibition is rapidly reversible, and they do not form more toxic oxons. Signs and symptoms of poisoning in general appear earlier, are usually less severe and recovery is more rapid. The pesticide with the lowest oral LD_{50}, aldicarb (Temik), belongs to this class of pesticide.

N-Methyl Carbamate Insecticides

Aldicarb (Temik)	Methomyl (Lannate)
Aminocarb (Matacil)	Oxamyl (Vydate)
Bendiocarb (Ficam)	Pirimicarb
Bufencarb (Bux)	Promecarb
Carbaryl (Sevin)	Propoxur (Baygon)
Carbofuran (Furadan)	Thiodicarb (Larvin)
Fenoxycarb (Torus)	Trimethacarb (Landrin)
Methiocarb (Mesurol)	

Signs and symptoms of N-methyl carbamate poisoning are the same as with the organophosphates, as is the antidote, atropine. 2-PAM is usually contraindicated since it can worsen poisoning. Cholinesterase test is often not as useful because cholinesterase regenerates so readily, often in the test tube on the way to the laboratory.

There have been no reported occupational deaths from N-methyl carbamates in the U.S., although aldicarb (Temik) may have contributed to the death of a California farm worker in a tractor roll over accident[201]. An occupational fatality from methomyl was reported in a farmer from Greece working in an enclosed space without proper protection[202].

Farm Worker Crew Poisonings. Farm worker crew poisonings are unusual with N-methyl carbamates because of the quick reversibility of cholinesterase inhibition, and the rapid resolutions of signs and symptoms. Two reported incidents from California are described in which cholinesterase testing, which is usually not very helpful in carbamate poisoning, proved of value in diagnosing and managing the illnesses.

Grape girdlers: methomyl. Twelve members of a crew of 16 workers developed nausea, vomiting, dizziness, headache, and abdominal pain while girdling[c] grapes in Kern County, California. Depressed or low normal levels of both red blood cell and plasma cholinesterase were found in 12 of 13 workers tested. Four hospitalized workers, discharged within 24 hours, had a 20% increase in RBC cholinesterase activity compared to samples taken eight to 12 hours earlier in the emergency room. Four days later, all workers had complete recovery of cholinesterase activity, which is consistent with of N-methyl carbamate poisoning. Methomyl was found on clothing samples form the hospitalized workers. Samples of dislodgeable residues from the grape leaves in the field showed a mean methomyl level of 0.27 $\mu g/cm^2$ on the day of the poisoning.

In a study five days later, mean methomyl residues of 0.065 $\mu g/cm^2$ and a peak of 0.125 $\mu g/cm^2$ were found. None of the workers tested had significant cholinesterase depression. The previously estimated "safe" level of 1.5 $\mu g/cm^2$ was clearly too high, and illness and cholinesterase depression occurred at much lower levels[203].

Cotton weeders: carbofuran. Thirty four workers became ill after entering a cotton field two hours after it had been sprayed with carbofuran. This insecticide has a 48 hour restricted entry interval on cotton, and requires both posting of treated fields and oral notification of workers after application.– neither was done. The crew ranged in age from 13 to 64 years (median 31) . The symptoms most commonly reported were nausea in 97% headache in 94%, eye irritation in 85%, muscle weakness in 82%, tearing in 68%, vomiting in 79%, and salivation (drooling) in 56%. The most commonly observed signs were bradycardia (heart rate less than 60) in 21%, diaphoresis (excess sweating) in 15%, and miosis (small pupils) in 12%.

Twenty-nine workers were released after decontamination and evaluation; one was hospitalized with new-onset atrial fibrillation. Four workers went home, showered, and did not seek medical care until three to 17 days later. Twenty-eight workers (82%) lost at least one day of work.

Plasma and red blood cell cholinesterase samples from 29 workers were all within normal limits but had not been

[c] "Girdling" is done to prevent sugars being transported to vine roots. Workers kneel or squat beneath the canopy of each vine trunk and interrupt the phloem layer of the vine trunk by cutting a 2-4 mm deep and 3 mm wide band around its circumference using a special curved, double-bladed knife designed for the task.

placed on ice after collection. Ten workers who had proper collection of red blood cell samples three hours later were lower than laboratory reference normal values. Urinary metabolites of carbofuran were detected by in 18 (58%) of 31 samples up to 11 days following the exposure.

The California Department of Health investigators concluded that since reliance on control measures may be inadequate, the substitution of safer, less toxic alternative pesticides should be adopted when feasible[204]. The investigator from the Department of Pesticide Regulation Worker Health and Safety branch concluded that the incident could have been prevented with appropriate communication and adherence to existing regulations on restricted entry intervals and field posting[205]

Watermelon Poisoning. On July 4, 1985, the largest outbreak of pesticide related food-borne illness in North America, was traced to the illegal use of aldicarb (Temik) on watermelon by certain farmers in Kern County, California. Of the 1,376 cases reported in California , 77% were classified as being probable or possible aldicarb poisoning. Seventeen people were hospitalized, and two of 47 pregnant women reported subsequent stillbirths, although aldicarb sulfoxide was not found in the fetuses at autopsy. Ten other jurisdictions reported 483 probable or possible cases: Alberta , Canada (20), Alaska (47), Arizona (one), British Columbia (206), Colorado (one), Hawaii (two), Idaho (80), Nevada (four), Oregon (104), and Washington State (18).

The most common signs and symptoms were nausea, vomiting, diarrhea, profuse sweating, excessive tearing, muscle fasciculations, and bradycardia, which occurred within a half an hour or less after eating the watermelon. More severe signs and symptoms included seizures, loss of consciousness, cardiac arrhythmia, hypotension, dehydration, and anaphylaxis. Estimated dose levels of adicarb sulfoxide were 0.0023- 0.06 mg/kg body weight, and most were well below the 0.025 mg/kg LOEL (Lowest Observed Effect Level) for subclinical RBC cholinesterase depression previously reported for humans [206,207,208,209].

Illegal Use of Aldicarb as a Rodenticide. Poisoning and fatalities have resulted from illegal use of aldicarb as a rodenticide, a use for which it is not registered. The cases in the U.S. were from a product called “Tres Pasitos” illegally imported from the Carribean[210,211,212,213].

Fate in the Body. Organophosphates and N-methyl carbamates are rapidly excreted from the body, primarily in the urine. They do not accumulate and are not stored in fatty tissue or breast milk.

Pyrethrum, Pyrethrins, Synthetic Pyrethroids

Pyrethrum and pyrethrins are natural compounds derived from a tropical chrysanthemum flower. Pyrethrum is made from the petals, and pyrethrins are chemicals extracted from the flower with solvents. Pyrethroids are man-made synthetic chemical analogues of pyrethrins.

Most are not highly acutely toxic and are unlikely to cause serious work related poisoning, since they are readily metabolized and excreted from the body.

It is not correct that only the natural plant based products are allergenic and not the synthetic pyrethroids. While it is true that the flower based natural products contain allergens that cross-react with ragweed and other pollens – both the natural and synthetic forms can cause allergies The group most at risk from exposure to this class of compounds are asthmatics.(see Table 5).

Pyrethrum, Pyrethrins and Synthetic Pyrethroids

Natural Compounds

Pyrethrum
Pyrethrins

Type I Synthetic Pyrethroids

Allethrin	Cyfluthrin
Bioallethrin	Permethrin
Bioresmethrin	Resmethrin
Biopermethrin	Tetramethrin
Cismethrin	

Type 2 Synthetic Pyrethroids

Cypermethrin	Fenothrin
Cyphenothrin	Flucythrinate
Deltamethrin,	Fluvalinate
Fenvalerate	Tralomethrin

Allergic rhinitis reactions to pyrethrum are frequent [214,215,216,217,218] .
Hypersensitivity pneumonitis was reported in a woman who used two and a half cans of pyrethrum-based insecticide in her home every week. She was hospitalized with fatigue, chest pain, coughing, and shortness of breath; a lung biopsy showed interstitial fibrosis. She recovered fully after supportive treatment, and remained asymptomatic after

discontinuing use of the insect spray. A pulmonary challenge test with the insecticide gave positive results, and a skin test with pyrethrum alone was positive[219].

A study of workers formulating pyrethrum powder found 30% had erythema, skin roughening, and pruritus, which subsided on cessation of exposure. One worker developed facial reddening, burning and itching, with rapid development of periorbital edema, and severe pruritus , which disappeared two days after removal from exposure[220].

Pyrethrins

Pyrethrins are in many over-the-counter products, especially aerosol sprays. A 24 year old man sprayed his dog and the floor of his bedroom with pyrethrin flea spray with no ventilation, rubbing the spray into the dog's fur with ungloved hands. Within an hour he developed shortness of breath, abdominal cramping, and vomiting. In the emergency room, his symptoms abated within two hours except for fatigue[221]. No information was reported about the dog. See section on asthma below for effects of pyrethrin shampoos.

Synthetic Pyrethroids

The synthetic pyrethroids are sodium channel toxins. They are divided into two groups depending on whether they have a cyano group (CN). The cyano group (CN) Type I pyrethroids are more toxic than the Type II without this group (see box). Animal studies show that Type I pyrethroids produce reflex hyperexcitability and fine tremor. Type II pyrethroids produce salivation, hyperexcitability, horeoathetosis, and seizures. Both types are potent activators of the sympathetic nervous system.

For commercial pesticides, the type II pyrethroids are more potent and more toxic than Type I. If type II poisoning advances to central hyper excitation, seizures can be difficult to control. Pyrethroids are also toxic to the nervous system, but are not cholinesterase inhibitors. The cyano groups pyrethroids are also more likely to cause the characteristic paraesthesia and dysesthesias (skin sensations of stinging, tingling itching, and numbness), lasting.18 to 24 hours and thought to be due to effects on from contact with sensory nerve endings[157]. Pyrethroids are readily metabolized and excreted, primarily in the urine. There are no biomarkers of exposure as there are for the organophosphates and N-methyl carbamates.

Table 5
Acute Pyrethroid Poisoning Signs and Symptoms

Dizziness	60.6%;
Headache	44.5 %
Nausea	59.7 %
Anorexia	45 %
Fatigue	26%
Vomiting	16%
Chest tightness	13.1 %
Parasthesia	11.89 %
Palpitation	13.1 %
Blurred vision	7 %
Increased sweating	6.% .

Source: Reference 193

A study of volunteers found significant differences in cyfluthrin metabolism in pesticide applicators. Those with a slower rate of metabolism had more symptoms from exposure than those with a faster rate of metabolism and excretion[222].

Hypersensitivity and allergic reactions are less common with the synthetic pyrethroids than with pyrethrum and the pyrethrins, but they do occur. A farmer using flumethrine as a sheep deep without using protective clothing developed abdominal pain, vomiting, fatigue, muscle aches, and polyarthralgia. Immunological testing revealed increased levels of IgE[223].

Nursery workers had imitative symptoms of the skin and upper respiratory tract in 73% of those exposed to fenvalerate, in 63% to permethrin (trans/cis 75/25) and in 33% for permethrin (trans/cis 60/40)[224].

Pyrethroid insecticides were found to be only very light cutaneous irritants or sensitizers in 82 workers patch tested with 1, 2, or 5% allethrin, cypermethrin, deltamethrin, fenothrin, fenvalerate, permethrin, and resmethrin. Two non-atopic workers had an irritant reaction to resmethrin. Of the two with allergic reactions to fenvalerate, one was a farmer with chronic hand dermatitis, and the other a hobby gardener[104].

A 59-year-old man who drank 600 ml of 20% permethrin developed vomiting and diarrhea soon after ingestion. in a suicide attempt. No clinical neurotoxicity such as tremor, hyper excitation, ataxia, convulsions, or paralysis occurred,

and he recovered with supportive treatment[225].

Pyrethroid fatality: Cypermethrin was the first pyrethroid reported to cause a human fatality. In Greece a man died three hours after eating a meal cooked in a 10% cypermethrin concentrate mistakenly used instead of oil. Nausea, prolonged vomiting with colicky pain, tenesmus, and diarrhea began within a few minutes, progressing to convulsions, unconsciousness, and coma. Death due to respiratory failure occurred despite intensive emergency treatment. Other family members developed less severe symptoms and survived[226].

Most of what we know about acute occupation poisoning from pyrethroids comes from a study of 292 Chinese farmers spraying deltamethrin, cypermethrin, and fenvalerate. Handling and hygienic practices were very poor, including use of higher concentrations than allowed, spraying for longer periods of time than recommended, clearing stoppages of equipment with mouth and hands, and not wearing personal protective equipment. Coarse muscular fasciculations developed in large muscles of extremities in the more serious cases. In those suffering from convulsions, seizures could occur up to 30 times a day in the first week. Most fully recovered in about six weeks[227].

Chlordimeform hemorrhagic cystitis
Severe illness occurred over a three day period in 1975 among nine workers packaging the cotton insecticide chlordimeform (Galecron) in a shed separate from other workers. They developed abdominal pain, dysuria, urgency to void, and hematuria (blood in the urine). Bladder biopsy specimens showed severe hemorrhagic cystitis. Three days after exposure, chlordimeform and 2-methyl-4-chloroaniline, a metabolite of chlordimeform, were present in the urine. The illness lasted from one week to two months[228].

Chlordimeform is readily absorbed through the skin of pesticide applicators. A study of urinary metabolites of 132 cotton applicators and handlers in California , found that despite the use of protective clothing and closed system transfer devices, chlordimeform metabolites were excreted in the urine. Mixer/loaders and equipment cleaning and maintenance workers had the greatest exposure [229]. Because of the adverse health effects seen in heavily exposed worker, cancerous tumors seen in mice, and the inability to protect workers from the risk of bladder cancer, chlordimeform was banned and the registrant voluntarily withdrew the registration in 1989[230,231.]

Deet Insect Repellent (N,N-diethyl-m-toluamide, OFF!)
Deet use in the U.S. is estimated to be about 200,000 applications per year[232]. Deet is more rapidly absorbed if the skin is sunburned, damaged, or irritated skin. It is excreted mostly in the urine, and does not accumulate in the body. Deet does cross the placenta; a study of 50 pregnant women who applied deet found the chemical in the cord blood of 8% of newborns[233]. There no specific antidote to poisoning. Treatment includes decontamination (removing contaminated clothing, washing the pesticide from the skin and hair, pumping it out of the stomach, if swallowed), seizure control, treatment of signs and symptoms, and support of respiration, blood pressure, and other body systems. There are no readily available blood or urine tests. See Chapter 7 for effects in children

Deet is a neurotoxin and toxic encephalopathy with seizures have been reported. Signs and symptoms of mild poisoning include headache, restlessness, irritability, and other changes in behavior. In more severe poisoning there can be slurring of speech, tremor (shakiness), convulsions, and coma. A 29-yr-old male suffered seizures eight to forty-eight hours following daily application to the skin daily from June through August[234], and a healthy adult male after topical application[235]. Neurologic signs and symptoms, including muscle cramping, insomnia, irritability, depression, and episodes of confusion were reported by National Park Service workers after exposure to 4 grams or more of deet per week [236]. Poisoning due to accidental or deliberate ingestion in 5 patients, aged one to 33, with two deaths[237]. Three cases following ingestion with complete recovery in all cases[238]

Cardiotoxicity has been reported in cases of severe poisoning in an adult male[239] , and in a 19 year old girl who attempted suicide by drinking 15-25 mls of a 95% formulation[240]. A study of 20,764 calls to poison control centers from 1993 to 1997 for exposures involving deet, in nearly 70% there were no exposure related symptoms. The highest rates of symptoms related to the eyes. There were two deaths, one in a 26-year-old male, and one in a 34-year-old female, both following skin application. Twenty-six reports involved major effects (0.13%). Although there were more reports involving infants and children, they had lower rates of adverse effects than teens or adults[241]

Fumigants

Fumigants are powerful poisons in the form of a gas that can severely injure any tissue they come into contact with. A review of 1,192 definite, probable, or possible cases of pesticide-related illnesses by the Washington State Department of Health from 1992-1996, found 39 cases related to fumigants (3.3%). The exposures were to aluminum phosphide (15), methyl bromide (12), metam-sodium (9), and zinc phosphide (3). Symptoms included respiratory problems and eye and/or skin irritation for the majority of exposures. No deaths were reported. The exposures were to applicators (17), reentry into a fumigated structure (9), improper storage or disposal (6), reentry into treated agricultural fields (4), drift from treated fields (2), and other (1).

Fumigants

Available Over-the-Counter

Dichlorvos (Pest Strips)
Metam-sodium (Vapam)
Paradichlorobenzene (mothballs)
Naphthalene (mothflakes)

Commercial Use Only

Aluminum phosphide (Phosphine)
Chloropicrin
1,3-Dichloropropene (Telone)
Methyl bromide
Sulfuryl fluoride (Vikane)

Methyl bromide. Methyl bromide can cause severe chemical burns which cannot be prevented by standard protective clothing[242]. A crew of six workers fumigating a 13th century castle developed erythematous skin with multiple vesicles and large bullae within 8 hours of exposure, primarily in the axillae, groin, vulva, scrotum, perineum, and umbilicus. The skin returned to normal in four weeks, except for some residual hyperpigmentation[243]. Severe poisoning has been reported in applicators not wearing adequate footwear[121].

Farm workers developed fatigue and light-headedness, respiratory, and gastrointestinal symptoms after removing polyethylene sheets from soil fumigated with methyl bromide four days earlier. Their symptoms resolved over several days, but neuropsychiatric symptoms persisted for several weeks.[244]. Workers fumigating crops for export experienced insomnia, headache, paresthesias, mood changes and loss of memory and concentration[245]. Toxic encephalopathy, toxic myoclonus[246,247,248, 249,250,251], and permanent neurological sequelae[252, 253,254] have been reported in survivors of acute methyl bromide poisoning[255].

Methyl bromide fatalities: There are many methyl bromide fatalities reported in the literature: a grain fumigation worker[256], a 19 year old pancake house manager who re-entered the restaurant too soon after it was fumigated[257], a 12 year old and a 23 year old who entered fumigated railroad cars[258], and four burglars who entered tented fumigated houses[259].

An unusual incident was the death of a young woman from methyl bromide seeping through underground conduits from a fumigated building to an adjacent guest house on the same property. She developed refractory seizures, intermittent fever, and multi-organ system failure before dying 19 days later[260]. A similar sad case was the death of a newborn baby 12 hours after a neighbor's house was fumigated. The sewage pipes serving the two houses had been sucked empty only one to two hours prior to the start of fumigation, resulting in an open sewage connection between the houses and permitting methyl bromide to leak from the treated house into the house of the affected family[261].

Victims of methyl bromide poisoning have a higher amount of inorganic bromide in their blood than the usual background level[262]. There are no specific biomarkers, and blood and urine tests are not readily available.

Sulfuryl fluoride (Vikane). Sulfuryl fluoride's primary use is in termite control, and agricultural is not a significant user. There are very few reports of non-fatal poisoning in humans even though it is a highly toxic gas.

A 30 year old man developed nausea, vomiting, abdominal cramping, pruritis, reddening of the conjunctivae, pharynx and nasal mucosa, and pin-prick anesthesia of the lateral border of one leg. after four hours exposure to sulfuryl fluoride in an unventilated room. He recovered in four days with supportive treatment[263].

An elderly couple was allowed to re-enter their home that had been fumigated with sulfuryl fluoride the day before, five hours after ventilation procedures were completed. Within 24 hours of their return, the wife developed weakness, nausea, and repeated vomiting. Her husband complained of restlessness, and dyspnea (difficulty breathing) which became progressively worse. The next morning he had a generalized seizure followed by

cardiopulmonary arrest, and died in the emergency room where he could not be resuscitated. Three days later his widow went to see her family doctor, complaining of severe weakness, dyspnea, intermittent chills, and anorexia; she was unable to walk into office. She was admitted to the hospital where a chest x-ray showed diffuse pulmonary infiltrates. She developed ventricular fibrillation and died the next day.

It was later determined that the pest control operator failed to measure the air concentration of gas inside the home before allowing the couple to return. Neither of the two workers who removed the tarpaulin and ventilated the house was licensed; they were working under the supervision of a certified supervisor who was not on the premises as the law required. Because the product used in the home was manufactured before the requirement for a certified applicator to be on the premises was made law, the statement for this requirement was not on the label (most regulations changes have a clause that allows the use of "existing stock"). Since "the label is the law' technically there was no violation of the law[264]

Herbicides

Herbicides kill plants by affecting chemical reactions and metabolic pathways that don't exist in human beings. Plant growth regulators (PGR) act like plant hormones and slow down or speed up growth. Many herbicides and PGRs can cause irritant effects in the eyes, skin, nose and throat. Some can also cause allergic reactions in sensitive individuals. In general, they are not highly toxic and are unlikely to cause serious poisoning under usual conditions of exposure with the great exception of paraquat.

Herbicides

Available Over-the-Counter

Aciflurofen (Goal)	Glyphosate (Roundup)
Atrazine	MCPA
Benefin	MCPP
2,4-D (Weed-b-Gon)	MSMA
2,4-DP	Napropamide (Devrinol)
DCPA (Dacthal)	Oryzalin (Surflan)
Dalapon	Sodium chlorate
Dicamba	Prometon
Diquat,	Trichlopyr
EPTC	Trifluralin (Treflan)
Fluazifop-butyl (Fusilade)	

Commercial Use

Bromacil (Hyvar)	Metolachlor
Bromethalin	Oxadiazon (Ronstar)
Cacodylic acid (organic arsenic)	Paraquat (Gramoxone)
Chlormequat	Pronamide (Kerb)
Chlorsulfuron (Telar, Glean)	Simazine
Dichlobenil (Casaron)	Sulfometuron-methyl (Oust)
Duron	Ttrifluralin (Treflan)

Paraquat (Gramoxone) is the most common cause of fatal herbicide poisoning, mostly through oral ingestion. It can be lethal in very small amounts when swallowed and is the pesticide most often used for suicide throughout the world[265,266,267,268,269,270,271,272,273,274]. Occupational fatalities have occurred in farmers and in a landscape maintenance worker from absorption through the skin[275,276,277,278,279]. Systemic poisoning could occur if a concentrated form gets in the eyes or on the skin, or if it is swallowed[280].

Any exposure to paraquat must be evaluated, even if several days have passed since the herbicide was ingested. Signs of lung deterioration is often a sign of impending fatality.

Despite animal toxicity similar to paraquat, diquat does not cause similar lung effects in human poisonings, and reported deaths have been from other causes. Poisoned patients who receive appropriate and timely treatment are virtually assured of complete recovery from most insecticide and herbicide poisonings.

Plant Growth Regulators

Daminozide (B-nine, Alar
Dikegulac sodium (Atrinal)
Ethephon (Ethrel)
Gibberellic acid
Maleic hydrazide
Mefluidide (Embark)
Naphthyleneacetic acid (NAA).

Deaths and long-term sequelae most often result from respiratory complications, which may occur as complications of the intoxication or from other constituents in the insecticide or herbicide formulation. Good supportive care with meticulous attention to, and anticipation of, respiratory complications is absolutely essential to prevent long-term squelae or death from hypoxia.

There is no specific antidote to poisoning. Treatment includes decontamination (removing contaminated clothing, washing the pesticide from the skin and hair, pumping it out of the stomach, if swallowed), treatment of signs and symptoms, and support of respiration, blood pressure, and other body systems.

Most herbicides are excreted into the urine within one to four days after exposure. They do not accumulate in the

body. There are no readily available blood or urine tests.

A problem with herbicide products is a false sense of security. Because in general they are not acutely toxic and do not cause immediate apparent illness, they are considered "safe". A concern with this group of chemicals is their chronic toxicity discussed in Chapters 5 and 7.

Fungicides

Fungi do not share any attributes with human beings; therefore, fungicides tend to have low acute toxicity for humans. Many are eye and skin irritants, and can cause skin rashes. As a group they are the most likely to cause allergic skin reactions, and can sensitize the skin at low levels (see Tables 1,2 and 5.

Fungicides

Aliette (Fosetyl-al)	Mancozeb
Anilazine (Dyrene)	Maneb
Benomyl (Benlate)	Metalaxyl (Ridomil
Captan	Oxycarboxin (Plantvax)
Chlorothalonil (Daconil,	PCNB
Bravo)	Piperalin (Pipron)
Copper compounds	Sulfur/lime sulfur
Dazomet (Basamid)	Thiabendazole
Dicloran (DCNA)	Thiophanate-methy
Fenarimol (Rubigan)	Thiram
Fenbutatin oxide	Triadimefon (Bayleton)
(Hexakis,Vendex)	Triforine (Funginex).
Iprodione	Vinclozolin (Ronilan).
Lime sulfur	

Because of their low acute toxicity, fungicides are unlikely to cause serious poisoning. Of the examples listed, thiram can cause an unusual reaction. It is chemically similar to antabuse, a pill taken by alcoholics who are trying to quit. If they drink while taking the pill they get nausea, vomiting, pounding headache, dizziness, difficulty breathing, abdominal pain, and profuse sweating, among other symptoms. The same problem is possible with thiram if used while drinking alcohol, but has only been reported in workers[281].

Most fungicides are poorly absorbed and excreted primarily in the urine; they do not accumulate in the body. There are no readily available blood and urine tests.

As with most herbicides, a problem with many fungicides is a false sense of security. Because they are not acutely toxic and do not cause immediate apparent illness they are considered to be "safe." The greater concern with this group of chemicals is their chronic toxicity which is discussed in Chapter 5.

Rodenticides

The anticoagulant rodenticides are blood thinners and cause internal bleeding. The aluminum, magnesium, and zinc phosphide fumigants form phosphine gas on contact with moisture in the air, which is a potent tissue toxin. Strychnine (a natural toxin also known as nux vomica) violently attacks the nervous system.

Rodenticides

Anticoagulants

Brodifacoum
Bomadiolone
Clorophacinone
Diphacinone
Pindone (Pival, Pivalyn).
Warfarin

Fumigants

Aluminum phosphide (Phostoxin)
Magnesium phosphide
Zinc phosphide

Botanical

Strychnine

The anticoagulants and strychnine are in the form of baits, in which the greatest risk of poisoning is from ingestion (swallowing). The anticoagulants can cause nosebleeds, bruises, and blood in the urine and stool depending on the amount ingested. If large amounts are swallowed it can be fatal.

Strychnine causes violent seizures (convulsions) which can cause asphyxiation and death. Phosphine gas released from zinc and magnesium phosphide causes severe irritation of the lungs. If the dose is high enough it can cause pulmonary edema (fluid in the lungs) which can be fatal.

Vitamin K_1 is the antidote to poisoning from anticoagulants rodenticides. There is no antidote to strychnine. Treatment includes seizure control, support of respiration, and kidney dialysis if needed. There is no antidote to phosphine. Management includes treatment of signs and symptoms, and support of respiration, blood pressure, and other body systems.

Except for the fumigants, most are poorly absorbed into the body and excreted primarily in the urine. They do not accumulate. The anticoagulants affect a clotting factor in the blood called prothrombin. The prothrombin time test determines when the clotting ability of the blood is back to normal. There are no readily available blood or urine

tests for strychnine or phosphine.

Chlorinated Hydrocarbons
DDT and related chemicals are no longer widely used in pest control, and many have been banned. Of those still on the market, endosulfan is the most toxic. Lindane is still available by prescription for headlice. The hallmark of poisoning with the chlorinated hydrocarbon pesticides is seizures (convulsions), which can occur without other symptoms. Milder poisoning is characterized by headache, dizziness, nausea, vomiting, incoordination, tremor, mental confusion, and jerky muscle movements (myoclonus).There is no specific antidote and treatment include removing contaminated clothing, washing the pesticide from the skin and hair, pumping it out of the stomach, if swallowed, seizure control, and support of respiration, and other body systems.

Most are readily absorbed through the skin and excreted in the urine and feces. Those in current use (see list above) are not stored in the body for any length of time, except for lindane metabolites α-HCH, and β-HCH. Dicofol is contaminated with DDT which does accumulate and stays in the body for many years. primarily in fat.

Detectable in the blood, but is not a routine test. Analysis is not necessary for treatment of poisoning and tests are done in most toxicology laboratories. Except for lindane, it is unlikely that residues will be found if the exposure occurred a week or more prior to the test, unless there were unusual exposure conditions.

Chlorinated Hydrocabon Insecticides

Still in Use in the U. S.

Dicofol (Kelthane)	Lindane
Dienochlor	Methoxychlor
Endosulfan	

No Longer Registered in the U.S.

BHC	Emdrin
Chlordane	Hexachlorobenzene
Chlorobenzilate	Kepone
DDT	Mirex
Dieldrin	Toxaphene

DDE, a metabolite of DDT is the most commonly found, but dieldrin, chlordane (transnonachlor), and hexachlorobenze are found in blood, fat, breast milk, and other body tissues. Chlorinated hydrocarbons pass from mother to fetus across the placenta, and are also found in semen and ovarian follicular fluid (see Chapter 6).

Inert Ingredients
Petroleum distillates, toluene, xylene, alcohols, glycols, ethers, and other solvents are added to pesticides to dissolve, emulsify, or stabilize them, or to facilitate spreading, sticking, and penetration of the pesticide. Many cause irritation of the eyes, mucus membranes and skin.

The greatest hazard is chemical pneumonia (also called hydrocarbon pneumonitis) from aspiration of even tiny amounts into the lungs. This can occur if the victim vomits, vomiting is induced or the stomach is pumped. Signs and symptoms of chemical pneumonia are fever, rapid heart beat, rapid breathing, and cyanosis (turns blue). This type of pneumonia can be fatal, and recovery can take several weeks.

Many inerts are chlorinated hydrocarbons that can cause damage to the liver, heart, and kidneys if swallowed. There is no specific antidote to poisoning. The standard tests should be done to determine if there is damage to the liver, heart, or kidneys.

Natural Substances
Abamectin is an antibiotic with a narrow spectrum of activity. Bacillus thuringiensis (BT) is a bacterium with exotoxins toxic to insects. These agents have a narrow spectrum of activity. That is, their toxicity is specific to the particular target pest they are being used against. They are the least likely to pose a human health hazard. However any product can potentially be an irritant or cause local skin reactions, or other acute reactions.

Diatomaceous earth is made from diatoms (fossils), and like **silica gel** kills insects by drying out the waxy coating on the insects' protective outer cover, called the cuticle. The diatomaceous earth registered for use as a pesticide is *not*

Natural Substances Used as Pesticides

Available Over-the-Counter
Arsenic
Avermectin / abamectin / ivermectin
Bacillus thuringiensis (Bt)
Boric acid
Diatomaceous earth
Neem (azadirachtin)
Silica gel (silicon dioxide

Commercial Use Only
Liquid nitrogen.
Nicotine (Black Leaf 40)

the same product as that used as a filtering agent in swimming pools. The swimming pool product is higher in free silica, the crystalline form that can cause scarring of the lungs (silicosis).

Neem is a tree oil from India that kills insects by unknown mechanisms.

Boric acid is a tissue and stomach poison if swallowed. Boric acid powders are not absorbed through the skin but can be mildly irritating (including borax). Any pesticide product can potentially cause skin irritation or rash in some individuals. Acute poisoning results from swallowing) the pesticide. If only a small amount is swallowed there may be no symptoms. Vomiting, abdominal pain, and diarrhea are common symptoms when they do occur. Boric acid is poorly absorbed through the skin and is excreted in the urine in about 24 hours. Borates (from boric acid) can be measured in the blood, serum, and urine.

Arsenic acts as a tissue poison by combining with sulfur and phosphate in proteins and enzymes, interfering with their normal function. Arsenic causes skin problems, but it is unlikely from home use. Acute poisoning results from swallowing the pesticide. The breath and feces can smell like garlic. There is abdominal pain, and watery diarrhea that might have blood in it. The nervous system, heart, liver, kidneys, and bone marrow can also be affected. BAL (dimercaprol) is an antidote to arsenic poisoning; D-penicillamine is another antidote that can be used if the victim is not allergic to penicillin. Arsenic is also excreted in the urine.

Nitrogen is a gas (78% of the air we breathe) which freezes when compressed into a liquid. It kills termites and other wood destroying insects by freezing them to death. An exterminator applying liquid nitrogen died from suffocation while working in an enclosed wall space without any ventilation. There is no danger to the home owner when the gas dissipates since it is a normal part of the air we breathe.

Nicotine is the most acutely toxic of the natural group of pesticides. It attacks the brain, nervous system, and nerve-muscle connections, but does not affect cholinesterase activity. The signs and symptoms of mild to moderate nicotine poisoning are very similar to those from nerve-gas type pesticides – excess salivation (drooling), nausea, vomiting, and miosis (small pupils). Severe poisoning results in muscle paralysis, shock (collapse of the heart and vascular system with drastic lowering of blood pressure), and respiratory paralysis. There is no specific antidote to nicotine poisoning, but atropine can control the excess secretions. Treatment in all cases includes decontamination (removing contaminated clothing, washing the pesticide from skin and hair, inducing vomiting or pumping the stomach if swallowed, treatment of signs and symptoms, and support of respiration, blood pressure, and other body systems. Nicotine is readily absorbed and is transformed by the liver into several simpler chemicals (metabolites) which are excreted into the urine within a few hours. Cotinine is the major metabolite in urine.

Pesticides and Asthma

Asthma is the most frequently diagnosed occupational lung disease, and typically signs and symptoms worsen on work days and improve on days off and holidays. Occupational asthma is also less frequently related to seasonal variations, exacerbation by allergies, pets and stress, or a family history of the disease[282]. Exposure to pesticides can trigger or exacerbate asthma, induce bronchospasm, or increase bronchial hyperreactivity. See Chapter 7 for a discussion of asthma in children related to pesticide exposure.

Table 5
Pesticides Linked to Asthma, Wheezing, and Hyperreactive Airway Disease

Antimicrobials
Bromine, hydrobromic acid
Chloramine-T
Chloramines
Chlorine
Quarternary ammonium
Fumigants
Ethylene oxide
Metam-sodium
Fungicides
Captafol
Chlorothalonil
Dithiocarbamates
Fluazinam
Tributyltin oxide
Inerts
Denatonium benzoate
Herbicides
Alachlor
Atrazine
EPTC
Paraquat
Insecticides
Carbofuran
Chlorpyrifos
Dichlorvo
Ethoprop
Insecticide aerosols
Insecticide coils
Malathion
Paraquat
Pyrethrins
Pyrethrum
Tetramethrin

Asthma and Occupational Exposure

Agricultural Exposures: Use of paraquat, parathion, chlorpyrifos, atrazine and alachlor were found to be related to wheezing in 3,889 farmer applicators. A significant dose response trend was found. Malathion and EPTC were also associated with wheeze, but did not show a dose response trend. There was no association with 2,4-D use[283].

A male Japanese farmer with recurrent episodes of dyspnea and wheezing for 10 years was found to have chlorothalonil induced asthma. Patch testing showed a positive but a specific IgE antibody twas not found. Entering a treated greenhouse produced dyspnea, wheezing, and a sharp drop in pulmonary function (FEV1). Bronchial challenge with 0.1% TCPN induced an early and late asthmatic response that lasted 48 hours[284].

Insecticide and fertilizer use in several villages in rural China was found to increase the risk of asthma-like symptoms[285].

Paraquat applicators on 15 Nicaraguan banana plantations with more than two years cumulative exposure had a three fold increase in episodic wheezing compared to workers who had never applied paraquat. Shortness of breath also occurred among the more intensely exposed workers. There was no relationship between exposure and pulmonary function findings[148]. A case report of asthma related to paraquat was reported from Italy[76].

A review of cases reported to the California Pesticide Illness Surveillance Program raised concerns of asthma potentially associated with exposure to contaminants in organophosphate insecticides[286].

A worker with contact sensitivity to captafol (Difolatan) was skin test positive, but his asthma was not exacerbated by exposure to the pesticide[57].

Aerial pesticide applicators had no difference in asthma prevalence compared to controls[287].

Pesticide Factory workers: No differences were found in bronchial hyperreactivity between factory workers exposed to pesticide dusts and controls[288]. After several years of exposure to captafol, a pesticide manufacturing worker had new onset of work-related asthma. He had a marked and persistent decrease in pulmonary function (FEV1) upon bronchial challenge with captafol. Removal from exposure resulted in improved symptoms and pulmonary function[289]. A report of two cases of occupational asthma in workers from the same pesticide plant, caused by sensitization to powdered fungicides fluazinam and chlorothaloni. The diagnosis in each case was confirmed by pulmonary function testing and bronchial challenge tests.[290].

Pest Control Operators: Six years after beginning work as a pest control operator, a 47 year old man developed asthma. He was forced to quit his job one year later. Challenge testing showed positive reaction to tetramethrin, which also caused a 30% drop in FEV1[291] . In one of the few studies to report mortality from asthma, outdoor workers exposed to pesticides in Australia were found to be at increased risk, SMR 3.45 (1.39-7.1)[292]

Other workers: Female nurses manifested asthma symptoms upon handling disinfectant solutions containing benzalkonium chloride. They had work related decreased pulmonary function, and positive response to bronchial challenge[293].

A cook who worked an eight hour shift in a closed room that had been treated the day before with dichlorvos, presented with progressive respiratory symptoms and wheezing eight days after the exposure. A decrease in serum cholinesterase activity was noted. Decreased pulmonary function was still present 20 days later. He developed severe cortisol dependent asthma cortisol treatment and one year was still unable to participate in sports[294].

Two women packaging Chloramine T dust developed bronchial asthma after several years exposure, and a male welder/equipment repair worker developed progressively severe dyspnea and wheezing with repeated exposure to Chloramine T dust equipment and containers. All three had s chloramine-T specific IgE antibodies in their serum and skin prick test reactions of greater than 2+[295]. A woman developed sneezing, coughing and dyspnea shortly after being use of a new disinfectant, chloramine-T, at work cleaning showers and saunas at a municipal indoor swimming

pool. She developed rhinorrhea, coughing, dyspnea and bronchial wheezing after provocation with 2 ug of the chemical[296]. Seven brewery workers developed asthmatic symptoms from exposure to chloramine disinfectant which resolved with removal from exposure. Skin tests produced a weak positive flare reaction[297].

A case report of a railway station repair worker who was exposed to high levels of ethylene-oxide (over 700 ppm) from a leak, developed coughing, shortness of breath, and wheezing after four days exposure. Three years later he had not change in his clinical respiratory state and pulmonary function[298]. Other reports in health care worker were in a nurse[299], and a surgeon induced by ethylene-oxide used to sterilize gloves[300].

A report of three cases of asthma caused by inert ingredient ethanolamine, confirmed by challenge testing Two were metal workers exposed to a cutting fluid containing triethanolamine, and the other a cleaner exposed to a detergent containing monoethanolamine. Persistence of the symptoms after exposure ended was a common feature of the three cases[301].

A previously healthy female venipuncture technician developed acute retrosternal chest pain, nausea, and lethargy within a few hours of arriving at work. The symptoms cleared when she took two days off, but recurred along with chest tightness, cough, and wheeze when she returned to work. Thirty six hours before her first episode, the carpet in her workplace, which had been flooded, was treated with a deodorizer /fungicide preparation that contained tributyltin oxide TBTO). Bronchial challenge testing with TBTO caused a 19% decrease in FEV1 within 1 hour. The asthma continued to recur at work and she quit her job[302].

Decreased risk: European animal farmers 20 to 44 years old in Denmark, Germany, Switzerland, and Spain were found to have a lower prevalence of wheezing, shortness of breath, and asthma than the general population[303].

Asthma - Nonoccupational and Household Exposure

Pyrethrins: A 43-yr-old woman with a history of asthma and ragweed allergy, experienced an anaphylactic reaction after using a pyrethrin lice shampoo. Periorbital edema appeared within an hour; the next morning, she developed shortness of breath, chest tightness, numbness and became unresponsive. She responded to treatment with naloxone, epinephrine, aminophylline, albuterol, methyl-prednisolone and prednisone[304].

Pyrethrin fatalities: A 36 yr old woman with a history of asthma developed severe shortness of breath five minutes after she began washing her dog with a 0.05% pyrethrin shampoo. Within five minutes she was in cardiopulmonary arrest and could not be resuscitated[305]. Another fatality from exposure to a pyrethrin insecticide was attributed to sudden irreversible bronchospasm[306]

A study of seven patients with asthma from exposure to a household aerosol insecticide spray found bronchial challenge with the insecticide produced chest tightness and a decrease in pulmonary function, but no changes in bronchial reactivity to inhaled histamine.[307]. A study of standard and low irritant insecticide formulations found that some aerosols trigger symptoms and impair lung function in asthmatics[308].

Household use: The use of mosquito coils inside the home was associated with an higher prevalence of asthma in a study in Durban, South Africa[309]. A survey in Hawaii found that those using household insecticides daily were 40% more likely to have asthma than nonusers[310]

Hot Tub: Two cases of acute pneumonitis followed by reactive airways dysfunction syndrome developed after bathing in a hot tub. A bromine disinfectant which releases hydrobromic acid was implicated as the underlying cause[311].

Dentamonium: A 30 yr old male developed asthma and pruritus after using an insecticidal spray (Pyrex). The same symptoms appeared with an alcoholic skin disinfectant (M-sprit) and other spirituous preparations denatured with denatonium benzoate (Bitrex). An open epicutaneous test (20 min) showed wheal and erythema to Pyrex, spirit and Bitrex diluted to 26 mg/l. The contact urticaria elicited by denatonium benzoate apparently was caused by an immunologic mechanism of the immediate hypersensitivity type[312].

Asthma and Environmental Exposure

Community residents near a potato field treated with Ethoprop which releases n-propyl mercaptan, a highly odorous and volatile gas as a degradation product, were surveyed for odor-related illness. An increase in asthma attacks (six week prevalence OR 6.0) was found[14].

A follow up study after a tank car spill of metam-sodium released methyisothiocyanate gas to surrounding communities. Follow-up studies found 20 cases of persistent irritant-induced asthma and 10 cases of persistent exacerbation of asthma[313].

Asthma and Swimming Pools

A study in New Zealand of communities near aerial spraying with Foray 48B(Bt), and follow up three months later in the same participants, found no increase in symptoms in previously diagnosed asthmatics.[314].

Chlorine reacts with bodily proteins to form chloramines, of which the most volatile and prevalent in the air above swimming pools is nitrogen trichloride. A study in lifeguards and a swimming instructor with asthma, showed a positive specific challenge to nitrogen trichloride at 0.5 mg/m^3, with negative challenges to chlorine released from sodium hypochlorite. Swimming-pool asthma due to airborne nitrogen trichloride can occur in workers who do not enter the water because of this chloramine in the air[315,316] A study of swimming pool lifeguards nitrogen trichloride could not rule out risk of exposure related transient bronchial hyperresponsiveness[317].

Significant ly higher bronchial response to histamine challenge was found in members of the Finnish swim team (48%) than controls (16%). Sputum eosinophilia was found in 21% of the swimmers and none of the controls. The authors conclude that long-term and repeated exposure to chlorine compounds in swimming pools during training and competition may contribute to bronchial hyperresponsiveness and airway inflammation in swimmers[318].

References

1. Reigart JR, et al. 1999. Recognition and Management of Pesticide Poisonings. Fifth Edition. USEPA 735-R-98-002. Office of Pesticide Programs., Washington DC 20460. http://www.epa.gov/pesticides/safety/healthcare.
2. California EPA. 2001 Pesticide Illness Surveillance Program reports. HS 1843. http://www.cdpr.ca.gov/docs/whs/2001pisp.htm
3. Padgitt S, et al. 1995. Agriculture pesticide exposure, safety precautions, and pesticide-attributed illnesses among Iowa farmers. Agricultural Health and Safety: Workplace, Environment, Sustainability, H. H. McDuffie, et al. (Eds); Lewis Publishers, Boca Raton, pp 189-193.
4. Peoples SA, et al. 1979. Occupational exposures to pesticides containing organoarsenicals in California. Vet Hum Toxicol 1(6):417-421.
5. Saunders D, et al. 1987. Outbreak of Omite-CR induced dermatitis among orange pickers in Tulare County, California. J Occ Med 29:409-413.
6. Hu X, et al. 1992. Dose related acute irritant symptom responses to occupational exposure to sodium borate dusts. Br J Ind Med 49(10):706-713.
7. Koksal N, et al. 2003. Apricot sulfurization: an occupation that induces an asthma-like syndrome in agricultural environments. Am J Ind Med 43(4):447-453.
8. Ames RG, et al. 1993. Community exposure to a paraquat drift. Arch Env Health 48(1):47-52.
9. Alexeeff GV, et al. 1994. Dose-response assessment of airborne methyl isothiocyanate (MITC) following a metam sodium spill. Risk Anal14(2):191-198.
10. O'Malley M, et al. 2001. Illness Related to Exposure to Metam-Sodium Byproducts in Earlimart, California in November 1999. HS-1808, 08-21-01. www.cdpr.ca.gov/docs/whs/pdf/hs1808.pdf
11. Varma DR, et al. T. 1993. The Bhopal accident and methyl isocyanate toxicity. J Toxicol Env Hlth 40(4):513-529.
12. Andersson N, et al. 1988. Exposure and response to methyl isocyanate: results of a community based survey in Bhopal. BJIM 45:469-475.
13. Andersson N, Ajani MK, Ahashabde S. 1990. Delayed eye and other consequences from exposure to methyl isocyanate: 93% follow up of exposed and unexposed cohorts in Bhopal. Br J Ind Med 47(8):553-558.
14. Ames RG, et al. 1991. Acute health effects from community exposure to N-propyl mercaptan from an ethoprop (Mocap)-treated potato field in Siskiyou County, California. Arch Env Health 46(4):213-217.
15. Goldman LR, et al. 1987. Acute symptoms in persons residing near a field treated with the soil fumigants methyl bromide and chloropicrin. West J Med 147(1):95-98.
16. Tabershaw IR, et al. 1966. Sequelae of acute organophosphate poisoning. J Occ Med 8:5-22.
17. Whorton D, et al. 1983. Persistence of symptoms after mild to moderate acute organophosphate poisoning among 19 farm field workers. J Toxicol Env Health 11(3):347-354.
18. Acquavella JF, et al. 1999. Human ocular effects from self-reported exposures to Roundup herbicides. Hum Exp Toxicol 18(8):479-486.
19. Goldstein DA, et al. 2002. An analysis of glyphosate data from the California Environmental Protection Agency Pesticide Illness Surveillance Program. J Toxicol Clin Toxicol 40(7):885-892.
20. Ames RG. 1991. Multiple-episode conjunctivitis outbreak among workers at a nut-processing facility. J Occ Med 33(4):505-509.
21. Cole DC, et al. 1997. Dermatitis in Ecuadorean farm workers. Contact Dermatitis 37(1):1-8.
22. Wesseling C, et al. 2001. Pesticide-related illness and injuries among banana workers in Costa Rica: a comparison between 1993 and 1996. Int J Occ Env Health 7(2):90-97.
23. McKeag D, et al. 2002. The ocular surface toxicity of paraquat. Br J Ophthalmol 86(3):350-351.
24. Sinow J, et al. 1973. Ocular toxicity of paraquat. Bull Environ Contam Toxicol 9(3):163-168.
25. Vlahos K, et al. 1993. Paraquat causes chronic ocular surface toxicity. Aust N Z J Ophthalmol 21(3):187-190.

26. Nirei M, et al. 1993. Ocular injury caused by Preeglox-L, a herbicide containing paraquat, diquat and surfactants. Jpn J Ophthalmol 37(1):43-46.
27. Kamel F, et al. 2000. Retinal degeneration in licensed pesticide applicators. Am J Ind Med 37(6):618-628.
28. Misra UK, et al. 1985. Some observations on the macula of pesticide workers. Hum Toxicol 4(2):135-145.
29. Campbell AM. 1952. Neurological complications associated with insecticides and fungicides. Brit Med J 2:415-417.
30. DeHaro L, et al. 1999.[Methamidophos intoxication: immediate and late neurological toxicity; two case reports]. Acta Clin Belg Suppl 1:64-67.
31. Geffray L, et al. 1995. [Retrobulbar optic neuritis caused by disulfiram (Esperal): a case (letter)]. Rev Med Interne 16(12):973.
32. Ishikawa S, et al. 1971. Eye disease induced by organic phosphorous insecticides. Nippon Ganka Gakkai Zasshi 71(1):841-851.
33. Peyresblanques J. 1969. [Eye burn due to gramoxone]. Bull Soc Ophtalmol Fr 69(11):928.
34. DeBleecker JL.1992. Transient opsoclonus in organophosphate poisoning. Acta Neurol Scand 86(5):529-531.
35. Hata S, et al. 1986. Atypical ocular bobbing in acute organophosphate poisoning. Arch Neurol 43(2):185-186.
36. Liang TW, et al. 2003. Supranuclear gaze palsy and opsoclonus after Diazinon poisoning. J Neurol Neurosurg Psychiat 74(5):677-679.
37. Pullicino P, Aquilina J.1989. Opsoclonus in organophosphate poisoning. Arch Neurol 1989 Jun;46(6):704-705.
38. Taylor JR, et al. 1976. Neurologic disorder induced by Kepone: preliminary report. Neurology 26(4):358.
39. Chavez CT, et al. 1985. Methyl bromide optic atrophy. Am J Ophthalmol 99(6):715-719.
40. Cavalleri F, et al. 1995. Methyl bromide induced neuropathy: a clinical, neuro-physiological, and morphological study [letter]. J Neur Neurosu Psych 58:383.
41. Deschamps D, et al. 1990. Toxicity of ethylene oxide on the lens and on leukocytes: an epidemiological study in hospital sterilisation installations. Br J Ind Med 47(5):308-313.
42. Jay WM, et al. 1982. Possible relationship of ethylene oxide exposure to cataract formation. Am J Ophthalmol 93(6):727-732.
43. Seligman , GR. 1986. HHE Report HETA 83-335-1618, Kendall Company, Augusta, Georgia.GRA&I, Issue 16, 1986
44. Pietsch RL, et al. 1972. Lens opacities and organophosphate cholinesterase-inhibiting agents. Am J Ophthal 73:236-242.
45. Dementi B. 1994. Ocular effects of organophosphates: a historical perspective of Saku disease. J App Tox 14(2):119-129.
46. Erickson LK, et al. 1992. Ophthalmic toxicology of anticholinesterases. In Ballantyne B, (ed). Clinical and Experimental Toxicology of Organophosphates and Carbamates. Butterworth-Heinemann, Ltd., Oxford, England, pp 180-194.
47. Kogure M, et al. 1975. Ocular symptoms induced by organic phosphorus insecticides. J Am Med Wom Assoc 30(10):420-422.
48. Wang AG, et al. 1999. Positron emission tomography scan in cortical visual loss in patients with organophosphate intoxication. Ophthalmol 106:1287-1291.
49. O'Malley MA. 1997. Skin reactions to pesticides. Occ Med: State of the Art Reviews 12(2):327-345.
50. Lamberg SI, et al. 1969. Bullous reaction to diethyl toluamide (DEET) resembling a blistering insect eruption. Arch Derm 100(5):582-586.
51. Reuveni H, et al. 1982. Diethyltoluamide-containing insect repellent: adverse effects in worldwide use. Arch Dermatol 118(8):582-583.
52. Maibach HI, et al. 1975. Contact urticaria syndrome: contact urticaria to diethyltoluamide (immediate-type hypersensitivity). Arch Derm 111:726-730.
53. VonMayenburg J, Rakoski J. 1983. Contact urticaria to diethyltoluamide. Cont Derm 9:171.
54. Wantke F, et al. 1996. Generalized urticaria induced by a diethyltoluamide-containing insect repellent in a child. Cont Derm 35(3):186-187.
55. McKinlay JR, et al. 1998. Vesiculobullous reaction to diethyltoluamide revisited. Cutis 62(1):44.
56. Selim S, et al. 1995. Absorption, metabolism, and excretion of N,N-diethyl- m-toluamide following dermal application to human volunteers. Fund Appl Toxicol 25(1):95-100.
57. Pronczuk DeGarbino JP, et al. 1983. Toxicity of an insect repellent: N-N-diethyltoluamide. Vet Hum Toxicol 25(6):422-423.
58. Fuchs T, et al. 1993. Is benzalkonium chloride a relevant contact allergen or irritant? Hautarzt 44(11):699-702.
59. Kanerva L, et al. 2000. Occupational allergic contact dermatitis from benzalkonium chloride. Cont Derm 42(6):357-358.
60. Dooms-Goossens A, et al. 1983. Allergic contact urticaria due to chloramine. Cont Derm 9(4):319-320.
61. Warin AP.1992. Allergic contact dermatitis from dazomet. Cont Derm 26(2):135-136.
62. Boonk Wjete al. 1981 A possible case of delayed hypersensitivity to ethylene oxide. Clin Exp Dermatol 6(4):385-390.
63. Bruynzeel DP, et al. 1993. Dermatitis in bulb growers. Cont Derm 2(1):11-15.
64. VanJoost T, et al. 1988. Sensitization to DD soil fumigant during manufacture. Cont Derm 18(5):307-308.
65. Nater JP, et al. 1976. Occupational dermatosis due to a soil fumigant . Cont Derm 2(4): 227-222.
66. Schuman SH, et al. 1985. An outbreak of contact dermatitis in farm workers. J Am Acad Derm 13(6):220-223.
67. Matushita T, et al. 1981. Cross reactions between some pesticides and the fungicide benomyl in contact allergy. Indus Health 19(2):77-83.
68. VanKetel WG . 1977. Sensitivity to the pesticide benomyl. Cont Derm 2(5):290-291.
69. Lisi P, et al. 1987. Irritation and sensitization potential of pesticides. Cont Derm 17(4):212-218.
70. Peluso AM, et al. 1991. Multiple sensitization due to bis-dithiocarbamate and thiophthalimide pesticides. Cont Derm 25(5):327.
71. Guo YL, et al. 1996. Prevalence of dermatoses and skin sensitisation associated with use of pesticides in fruit farmers of southern Taiwan. Occ Env Med 53(6):427-431.
72. Mark KA, et al. 1999. Contact and photoallergic contact dermatitis to plant and pesticide allergens. Arch Dermatol 135(1):67-70.
73. Brown R. 1984. Contact sensitivity to Difolatan (Captafol). Cont Derm 10(3):181-182.
74. Verberk MM, et al. 1990. Health effects of pesticides in the flower-bulb culture in Holland. Med del Lavoro 81(6):530-541.
75. Vilaplana J, et al. 1993. Captan, a rare contact sensitizer in hairdressing. Cont Derm. 29(2):107.
76. Dannaker CJ, et al. 1993. Contact urticaria and anaphylaxis to the fungicide chlorothalonil. Cutis 52(5):312-315.
77. Horiuchi N, et al. 1980. Contact dermatitis due to pesticides for agricultural use. Nippon Hifuka Gakkai Zasshi (Jpn J Dermatol) 90(3):289.
78. Horiuchi N, et al. 1977. Studies on diagnostic standards on dermatitis due to pesticides, Part 4. Nippon Noson Igakkai Zasshi 26(3): 566-567.
79. Matsushita S, et al. 1996. Photoallergic contact dermatitis due to Daconil. Cont Derm 35(2):115-116.
80. Penagos HG. 2002. Contact dermatitis caused by pesticides among banana plantation workers in Panama. Int J Occ Env Health 8(1):14-18.
81. Meding B. 1986. Contact dermatitis from tetrachloroisophthalonitrile in paint. Con Derm 15(3):187.
82. Norris PG, et al. 1988. Photoallergic contact dermatitis from fentichlor. Cont Derm 18(5):318-320.
83. Pevny I. 1980. [Pesticide allergy - allergic contact eczema of a vintner]. Dermatosen Beruf Umwelt. 28(6):186-189.
84. VanGinkel CJ, et al. 1995. Allergic contact dermatitis from the newly introduced fungicide fluazinam.. Cont Derm 32(3):160-162.
85. Cole DC, Carpio F, Math JJ, et al. 1997. Dermatitis in Ecuadorean farm workers. Cont Derm 37(1):1-8.
86. Assini R, Fracchiolla F, Ravalli C, et al. 1994. [Allergic diseases caused by pesticides: 3 case reports]. Med Lav 85(4):321-326.
87. Cole DC, et al. 1997. Dermatitis in Ecuadorean farm workers. Cont Derm 37(1):1-8.
88. Piraccini BM, et al. 1991. A case of allergic contact dermatitis due to the pesticide maneb. Cont Derm 24(5):381-382.

89. Higo A, et al. 1996. Photoallergic contact dermatitis from mancozeb, an agricultural fungicide. Cont Derm 35(3):183.
90. Iliev D, et al. 1997. Allergic contact dermatitis from the fungicide Rondo-M and the insecticide Alfacron. Cont Derm 36(1):51.
91. Crippa M, Misquith L, Lonati A, et al. 1990. Dyshidrotic eczema and sensitization to dithiocarbamates in a florist. Cont Derm 23(3):203-204.
92. Nater JP, Terpstra H, Bleumink E. 1979. Allergic contact sensitization to the fungicide maneb. Cont Derm 5(1):24-26.
93. Koch P. 1996. Occupational allergic contact dermatitis and airborne contact dermatitis from 5 fungicides in a vineyard worker. Cont Derm 34(5):324-329.
94. O'Malley M, et al. 1995. Pesticide patch testing: California nursery workers and controls. Cont Derm 32(1):61-63.
95. Nishioka K, et al. 2000. Contact allergy due to propineb. Contact Derm 43(5):310.
96. Matsushita T,et al. 1975. Skin disorders caused by herbicides sodium chlorate and sodium 2,2-dichloropropionate. Kumamoto Med J 28(4):164-169.
97. Saunders H, et al. 2001. Allergic contact dermatitis due to thiuram exposure from a fungicide. Australas J Derm 42(3):217-218.
98. Ueda A, et al. 1994. Delayed-type allergenicity of triforine (Saprol). Cont Derm 31(3):140-45.
99. Horiuchi N, Ando S, Kambe Y. 1980. Dermatitis due to pesticides for agricultural use. Nippon Hifuka Gakkai Zasshi (Jpn. J. Dermatol.) 90(3):277.
100. Foussereau J, et al. 1982. Agriculture. In: Occupational contact dermatitis, clinical and chemical aspects. Copenhagen, Munksgaard, pages 90-100.
101. Schubel F, et al. 1971. [Inhalation allergy induced by the fungicide "Zineb 80"]. Deutsche Gesundheitswesen 26(25):1187-1189.
102. Ducombs G, et al. 1990. Allergic contact dermatitis and depigmentation due to a herbicide Lasso (alachlor). Cont Derm 23 (4):271.
103. Won JH, et al.1993. Allergic contact dermatitis from the herbicide alachlor. Cont Derm 28(1):38-39.
104. Spencer MC. 1966. Herbicide dermatitis. JAMA 198(12):1307-1308.
105. Pentel MT, et al. 1994. Allergic contact dermatitis from the herbicides trifluralin and benefin. J Am Acad Derm 31(6):1057-1058.
106. Bruze M, et al. 1982. Allergic contact dermatitis to chloridazon. Cont Derm 8(6):427.
107. Leow YH, et al. 1996. Allergic contact dermatitis from norflurazon (Predict). Cont Derm 35(6):369-370.
108. Horiuchi N,et al. 1977. Clinical symptoms of dermatitis due to pesticides, especially its relationship with sunlight dermatitis. Nipp Noson Igakkai Zasshi (J Jpn Assoc Rural Med) 26(1):87-88.
109. Koch P, et al. 1989. [Photoallergic dermatitis caused by the herbicide phenmedipham]. Derm Beruf Umwelt 37(6):203-205.
110. Farkasdy J, et al. 1976. A study on occupational dermatosis caused by Satecid 65 WP, a selective herbicide. Borgyogy Venerol. Sz. 52(3):112-113.
111. Schubert H. 1979. Allergic contact dermatitis due to propachlor. Dermatol Monatsschr 165(7):495-498.
112. Hogan DJ, et al. 1985. Allergic contact dermatitis due to a herbicide Barban. Can Med Assoc J 132(4):387-389.
113. Schena D, et al. 1992. Erythema multiforme-like contact dermatitis from dimethoate. Cont Derm 27(2): 116-117.
114. Lisi P. 1992. Sensitization risk of pyrethroid insecticides. Cont Derm 26(5):349-350.
115. Wakelin SH, et al. 1998. Allergic contact dermatitis from d-limonene in a laboratory technician. Cont Derm 38(3):164-165.
116.Karlberg AT, et al. 1997. Contact allergy to oxidized d-limonene among dermatitis patients. Cont Derm 36(4):201-206.
117. Chang YC, et al. 1997. Allergic contact dermatitis from oxidized d-limonene. Cont Derm 37(6):308-309.
118. Willems PW, et al. 1997. Allergic Contact dermatitis due to methiocarb (Mesurol). Cont Derm 36(5):270.
119. Bruynzeel DP. 1991. Contact sensitivity to Lannate. Cont Derm 25(1):60-61.
120. Paulsen E, et al. 1997. Concomitant sensitization to lannate and gerbera. Cont Derm 37(3):128-129.
121. Garcia-Bravo B, et al. 1995. Airborne erythema-multiforme-like eruption due to pyrethrum. Cont Derm 33(6):433.
122. Mitchell JC, et al. 1972. Allergic contact dermatitis from pyrethrum (Chrysanthemum spp.). Br J Dermatol 86(6):568-573.
123. Corazza M, et al. 1998. A goldsmith with occupational allergic contact dermatitis due to ethylenediamine in a detergent. Cont Derm 38(6):350-351.
124. Corazza M, et al. 1994. Occupational contact sensitization to ethylenediamine in a nurse. Cont Derm 31(5):328-329.
125. Cyrkunov LP. 1987. Toxico-allergic dermatitis due to ethylenediamine in herbicide (zineb) production. Gig Truda I Profess Zabolevanija 8:45-46.
126. Vozmediano JM, et al.. 2000. Immunologic contact urticaria from diethyltoluamide. Int J Dermatol 39(11):876-877.
127. Hayes WJJr, Laws ERJr.1991. Deet In: Handbook of Pesticide Toxicology. Vol 3. New Yor: Academic Press, Inc. p 1503.
128. Taylor JS, Lloyd KM. 1982. Chloracne from 3,3',4,4'-tetrachloroazoxybenzene and 3,3',4,4'-tetrachloroazobenzene update and review. In: Chlorinated Dioxins and Related Compounds, pp 535-544.
129. Sehgal VN, et al. 1983. Fume inhalation chloracne. Dermatologica 167(1):33-36.
130. Cheng WN, et al. 1993. A health survey of workers in the pentachlorophenol section of a chemical manufacturing plant. Am J Ind Med 24(1):81-92.
131. Cole GW, et al. 1986. Chloracne from pentachlorophenol-preserved wood. Cont Derm 15(3):164-168.
132. Jirasek L, et al. 1976. [Chloracne, porphyria cutanea tarda, and other poisonings due to the herbicides]. Hautarzt 27(7):328-333.
133. Morse DL, et al. 1979. Propanil-chloracne and methomyl toxicity in workers of a pesticide manufacturing plant. Clin Toxicol 15(1):13-21
134. Moretto A. 1991. Indoor spraying with the pyrethroid insecticide lambda-cyhalothrin. Bull WHO 69(5):591-594.
135. Tucker SB, et al.1983. Cutaneous effects from occupational exposure to fenvalerate. Arch Toxicol 54(3):195-202.
136. Flannigan SA, et al. 1985. Synthetic pyrethroid insecticides: a dermatological evaluation. Br J Ind Med 42(6):363-372.
137. Knox JM 2d, Tucker SB, Flannigan SA. 1984. Paresthesia from cutaneous exposure to a synthetic pyrethroid insecticide. Arch Dermatol 120(6):744-746.
138. Knox JM 2d, Tucker SB, Flannigan SA. 1984. Paresthesia from cutaneous exposure to a synthetic pyrethroid insecticide. Arch Dermatol 120(6):744-746.
139. Brenner S, et al. 2001. Pemphigus vulgaris: environmental factors. Int J Dermatol 40(9):562-569.
140. Lambert J, et al. 1986. Skin lesions as a sign of subacute pentachlorophenol intoxication. Acta Derm Venereol (Stockh) 66(2):170-172.
141. Orion E, et al. 2000. Pemphigus vulgaris induced by diazinon and sun exposure. Dermatology. 201(4):378-379.
142. Tsankov N, et al. 1998. Contact pemphigus induced by dihydrodiphenyltrichlorethane. Eur J Dermatol 8(6):442-443.
143. Vozza A, et al. 1996. Contact pemphigus Int J Derm 35(3):199-201.
144. Ducombs G, et al. 1990. Allergic contact dermatitis and depigmentation due to a herbicide Lasso (alachlor). Cont Derm 23 (4):271. [No
145. Brancaccio RR, et al. 1977. Contact dermatitis and depigmentation produced by the herbicide Carbyne. Cont Derm 3(2):108-109.
146. VanJoost T, et al. 1988. Sensitization to DD soil fumigant during manufacture. Cont Derm 18(5):307-308.
147. George AO. 1989. Contact leucoderma from paraquat dichloride? Cont Derm 20(3):225.
148. Cellini A, et al. 1994. An epidemiological study on cutaneous diseases of agricultural workers authorized to use pesticides. Dermatology 189(2):129-132.
149. Lisi P, et al. 1985. Pellagroid dermatitis from mancozeb with vitiligo. Cont Derm 13(2):124-125.
150. Sabouraud S, et al. 1997. Occupational depigmentation from dinoterbe. Cont Derm 36(4):227.
151. Penagos H, et al. 1996. Chlorothalonil, a possible cause of erythema dyschromicum perstans . Cont Derm 35(4):214-218.
152. Baran RL. 1974. Nail damage caused by weed killers and insecticides. Arch. Dermatol 110(3):467.
153. Baran MR 1973. Contact onychopathy due to synthetic organic pesticides: a case history involving DNOC. Bull Soc Fr Dermatol Syphiligr 80(2):172-173.

154. Botella R, et al. 1985. Contact dermatitis to paraquat. Cont Derm 13(2):123-124.
155. Bruynzeel DP. 1997. Bulb dermatitis. Dermatological problems in the flower bulb industries . Cont Derm 37(2):70-77.
156. Castro-Gutierrez N et al. 1997. Respiratory symptoms, spirometry and chronic occupational paraquat exposure. Scand J Work Env Health 23(6):421-427.
157. Howard JK. 1979. A clinical survey of paraquat formulation workers. Br J Ind Med 36(3):220-223.
158. Poskitt LB, et al. 1994. Chloracne, palmoplantar keratoderma and localized scleroderma in a weed sprayer. Clin Exer Dermatol 1(3):264-267.
159. Centers Disease Control. 1986. Outbreak of severe dermatitis among orange pickers - California. MMWR 35:465-467.
160. Saiz S, et al. 1986. Degradation of Propargite residues on orange foliage in Tulare County, California May-June 1986. California Dept. Food and Agriculture. Worker Health and Safety Branch. Sacramento CA 95814. www.cdpr.ca.gov/docs/whs/pdf/hs1408.pdf
161. California EPA. 2002. Guidelines for physicians who monitor workers exposed to cholinesterase-inhibiting pesticides. 4th Edition. Oakland, CA. www.oehha.ca.gov/pesticides/pdf/docguide2002.pdf
162. Cole TB, et al. 2003. Expression of human paraoxonase (PON1) during development. Pharmacogenetics 13(6):357-364
163. Akgur SA, et al. 2003. Human serum paraoxonase (PON1) activity in acute organophosphorous insecticide poisoning. Forensic Sci Int 133(1-2):136-140.
164. Costa LG, et al. 2003. Functional genomic of the paraoxonase (PON1) polymorphisms: effects on pesticide sensitivity, cardiovascular disease, and drug metabolism. Ann Rev Med 54:371-392.
165. Winterlin WL, et al. 1978. Dislodgable residues of dialifor and phosalone and their oxygen analogs following a reported worker-injury incident in the San Joaquin Valley, California. Bull Env Contam Toxicol 20(2):255-260.
166. Cowan J, et al. 2001. Gene therapy to prevent organophosphate intoxication. Toxicol Appl Pharmacol 173(1):1-6.
167. Jarvik GP, et al. 2003. Paraoxonase activity, but not haplotype utilizing the linkage disequilibrium structure, predicts vascular disease. Arterioscler Thromb Vasc Biol 23(8):1465-1471.
168. Kelada SN, et al. 2003. Paraoxonase 1 promoter and coding region polymorphisms in Parkinson's disease. J Neurol Neurosurg Psychiat 74(4):546-547.
169. DeBleecker J, 1993. Intermediate syndrome in organophosphorus poisoning: a prospective study. Crit Care Med 21(11):1706-1711.
170. DeBleecker J, et al. 1992. The intermediate syndrome in organophosphate poisoning: presentation of a case and review of the literature. J Toxicol Clin Toxicol 30(3):321-329.
171. DeBleecker J, et al. 1992. Intermediate syndrome due to prolonged parathion poisoning. Acta Neurol Scand 86(4):421-424.
172. De Bleecker J, et al. 1992. Prolonged toxicity with intermediate syndrome after combined parathion and methyl parathion poisoning. J Toxicol Clin Toxicol 30(3):333-345. Erratum: JTCT 1992;30(4):697.
173. Choi PT, et al. 1998. The use of glycopyrrolate in a case of intermediate syndrome following acute organophosphate poisoning. Can J Anaes 45:337-340.
174. He F, et al. 1998. Intermediate myasthenia syndrome following acute organophosphates poisoning – an analysis of 21 cases. Hum Exp Toxicol 7(1):40-45.
175. Qin F, et al. 1997. [Intermediate syndrome after acute organophosphorus pesticides poisoning]. Chung Hua Nei Ko Tsa Chih 36(9):613-616.
176. Nisse P, et al. 1998. Intermediate syndrome with delayed distal polyneuropathy from ethyl parathion poisoning. Vet Hum Toxicol 40(6):349-352.
177. Volk O, et al. 2002. [Attempted suicide by intravenous injection of metasystox]. Anasthesiol Intensivmed Notfallmed Schmerzther 37(5):280-283.
178. Avasthi G, et al. 2000. Serial neuroelectrophysiological studies in acute organophosphate poisoning–correlation with clinical findings, serum cholinesterase levels and atropine dosages. J Assoc Physicians India 48(8):794-799.
179. John M, et al. 2003. Muscle injury in organophosphorous poisoning and its role in the development of intermediate syndrome. Neurotoxicol 24(1):43-53.
180. Khan S, et al. 2001. Neuroparalysis and oxime efficacy in organophosphate poisoning: a study of butyrylcholinesterase. Hum Exp Toxicol 20(4):169-174.
181. Mani A, et al. 1992. Type II paralysis or intermediate syndrome following organophosphorous poisoning. J Assoc Physicians India 40(8):542-544.
182. Vaidya SR, et al. 2002. Life threatening stridor due to bilateral recurrent laryngeal nerve palsy as an isolated manifestation of intermediate syndrome. J Assoc Physicians India 50:454-455.
183. Benslama A, et al. 1998. [Intermediary syndrome in acute malathion poisoning]. Presse Med 27(15):713-715.
184. Groszek B, et al. 1995. Intermediate syndrome in acute fenitrothion poisoning. Przegl Lek 52(5):271-274.
185. Routier RJ, et al. 1989. Difficulty in weaning from respiratory support in a patient with the intermediate syndrome of organophosphate poisoning. Crit Care Med 17(10):1075-1076
186. Karalliedde L, et al. 1988. Acute organophosphorus insecticide poisoning in Sri Lanka. Forensic Sci Int 36(1-2):97-100.
187. Peiris JB, et al. 1988. Respiratory failure from severe organophosphate toxicity due to absorption through the skin. Forensic Sci Int 36:251-253.
188. Senanayake N, et al. 1987. Neurotoxic effects of organophosphorus insecticides. New Eng J Med 316:761-763.
189. Sungur M, et al. 2001. Intensive care management of organophosphate insecticide poisoning. Crit Care 5(4):211-215..
190. Sudakin DL, et al. 2000. Intermediate syndrome after malathion ingestion despite continuous infusion of pralidoxime. J Toxicol Clin Toxicol 38(1):47-50.
191. Parker PE, Brown FW. 1989. Organophosphate intoxication: hidden hazards. South Med J 82(11):1408-1410.
192. Guadarrama-Naveda M, et al. 2001. Intermediate syndrome secondary to ingestion of chlorpiriphos. Vet Hum Toxicol 43(1):34.
193. Midtling JE, et al. 1985. Clinical management of field worker organophosphate poisoning. West J Med 142(4):514-518.
194. Midtling J, et al. 1985. Acute poisoning following exposure to an agricultural insecticide California. MMWR 34(30):464-466,471.
195. McClure CD. 1976. Public health concerns in the exposure of grape pickers to high pesticide residues in Madera County, Calif., September 1976. Pub Health Rep 93(5):421-425.
196. Peoples SA, e tal. 1978. Organophosphate pesticide poisoning. West J Med 129:273-277.
197. O'Malley MA, et al. 1990. Subacute poisoning with phosalone, an organophosphate insecticide. West J Med 153(6):619-624.
198. Skeers VM , Morrissey B. 1995. Acute organophosphate poisonings in Washington apple orchards. J Env Health 5(2):18-23.
199. Geller RJ, et al. 2001. Nosocomial poisoning associated with emergency department treatment of organophosphate toxicity–Georgia, 2000. MMWR 49(51 & 52):1156-1158.
200. Koksal N, et al. 2002. Organophosphate intoxication as a consequence of mouth-to- mouth breathing from an affected case. Chest 122(2):740-741.
201. Lee MH, et al. 1984. A farm worker death due to pesticide toxicity: a case report. J Toxicol Env Health 14:239-246.
202. Tsatsakis AM, et al. 2001. Acute fatal poisoning by methomyl caused by inhalation and transdermal absorption. Bull Env Contam Toxicol 66(4):415-420..
203. O'Malley M, et al. 1991. Illness among grape girdlers associated with dermal exposure to methomyl. HS-1604, 05-02-91. www.cdpr.ca.gov/docs/whs/pdf/hs1604.pdf
204. Das R, et al. 1999. Farm worker illness following exposure to carbofuran and other pesticides - Fresno County, California 1998. MMWR 48(6):113-116.
205. Edmiston S, et al. 1999. Exposure and illness following early reentry into a carbofuran treated field. HS-1779. www.cdpr.ca.gov/docs/whs/pdf/hs1779.pdf
206. Centers Disease Control. 1986. Aldicarb food poisoning from contaminated melons - California. MMWR 35(16):254-258.
207. Goldman LR, et al. 1990. Pesticide food poisoning from contaminated watermelons in California, 1985. Arch Env Health 45(4):229-236.

208. Goldman LR, et al. 1990. Aldicarb food poisonings in California, 1985-1988: toxicity estimates for humans. Arch Env Health 45(3):141-147. [erratum AEH 1990 Nov-Dec;45(6):following 380].
209. Green MA, et al. 1987. An outbreak of watermelon-borne pesticide toxicity. Am J Pub Health 77(11):1431-1434.
210. Centers Disease Control. 1997. Poisonings associated with illegal use of aldicarb as a rodenticide—New York City, 1994-1997. MMWR (41):961-963.
211. Lima JS, et al. 1995. Poisoning due to illegal use of carbamates as a rodenticide in Rio de Janeiro. J Toxicol Clin Toxicol 33(6):687-690.
212. Nelson LS, et al. 2001. Aldicarb poisoning by an illicit rodenticide imported into the United States: Tres Pasitos. J Toxicol Clin Toxicol 39(5):447-452.
213. Ragoucy-Sengler C, et al. 2000. Aldicarb poisoning. Hum Exp Toxicol 19(12):657-662.
214. Rickett FE, et al. 1973. Pyrethrum dermatitis. II. The allergenicity of pyrethrum oleoresin and its cross-reactions with the saline extract of pyrethrum flowers. Pestic Sci 4(6):801-810.
215. Carlson JE, 1977. Hypersensitivity pneumonitis due to pyrethrum. JAMA 237(16):1718-1719.
216. Mitchell JC, et al. 1971. Allergic contact dermatitis from sesquiterpenoids of the Compositae family of plants Br J Dermatol 84(2):39-150.
217. Mitchell JC, et al. 1972. Allergic contact dermatitis from pyrethrum (Chrysanthemum spp.). The roles of pyrethrosin, a sesquiterpene lactone, and of pyrethrin II. Br J Dermatol 86(6):568-573.
218. Santucci B, et al. 1992. Occupational contact dermatitis to plants. Clin Dermatol 10(2):157-165.
219. Baer RL, et al. 1973. The most common contact allergens. Arch Dermatol 108(1): 74-78.
220. Zenz C ,et al. 1994. Case report - pyrethrums. Occupational Medicine 3rd ed. St. Louis, MO, p 641.
221. Paton DL, et al. 1988. Pyrethrin poisoning from commercial strength flea and tick spray. Am J Emerg Med 6(3):232-235..
222. Leng G, et al. 1999. Role of individual susceptibility in risk assessment of pesticides. Occ Env Med 56(7):449-453.
223. Box SA, et al. 1996. A systemic reaction following exposure to a pyrethroid insecticide. Hum Exp Toxicol 15(5):389-390.
224. Kolomodin-H B, et al. 1982. Occupational exposure to some synthetic pyrethroids (permethrin and fenvalerate). Arch Toxicol 50:27-33.
225. Gotoh Y, et al. 1998. Permethrin emulsion ingestion: clinical manifestations and clearance of isomers. J Toxicol Clin Toxicol 36(1-2):57-61.
226. Hayes WJJr, Laws ERJr (eds.). 1999. Handbook of Pesticide Toxicology. Vol. 2. Classes of Pesticides [p.597]. New York, NY: Academic Press Inc
227. He F, et al. 1989. Clinical manifestations and diagnosis of acute pyrethroid poisoning. Arch Toxicol 63:54-58.
228. Folland DS, et al. 1978. Acute hemorrhagic cystitis. Industrial exposure to the pesticide chlordimeform. JAMA 239:1052-1055.
229. Kurtz PH, et al. 1987. Assessment of potential acute health effects in agricultural workers exposed during the application of chlordimeform. J Occ Med 29:592-595.
230. Maddy KT, et al.. 1986. Monitoring the urine of pesticide applicators for residues of chlordimeform and its metabolites 1982-1985. Toxicol Lett 33:37-44.
231. Popp W, et al. 1992. Incidence of bladder cancer in a cohort of workers exposed to 4-chloro-o-toluidine while synthesizing chlordimeform. Br J Ind Med 49:529-531.
232. Landers SJ. 2003. DEET guidelines make for a safe summer. amednews.com June 16, 2003.
233. McGready R, et al. 2001. Safety of the insect repellent N,N-diethyl-M-toluamide (DEET) in pregnancy. Am J Trop Med Hyg 65(4):285-289
234. Centers Disease Control. 1989. Seizures temporally associated with use of DEET insect repellent--NewYork and Connecticut. MMWR 38(39):678-680.
235. Hampers LC, et al. 1999. Topical use of Deet insect repellent as a cause of severe encephalopathy in a healthy adult male. Acad Emerg Med 6(12):1295-1297.
236. Robbins PJ, et al. 1986. Review of the biodistribution and toxicity of the insect repellent N,N-diethyl-m-toluamide (DEET). J Tox Env Health 18(4):503-525.
237. Tenenbein M. 1987. Severe toxic reactions and death following the ingestion of diethyltoluamide- containing insect repellents. JAMA 258(11):1509-1511.
238. Tenenbein M. 1981. Toxic encephalopathy due to insect repellant ingestion. Vet Hum Toxicol 23(5):363.
239. Clem JR, et al. 1993. Insect repellent (N,N-diethyl-m-toluamide) cardiovascular toxicity in an adult. Ann Pharmacother 27(3):289-293.
240. Fraser AD, et al. 1995. Analysis of diethyltoluamide (DEET) following intentional oral ingestion of Muscol J Anal Toxicol 19(3):197-199.
241. Bell JW, et al. 2002. Human exposures to N,N-diethyl-m-toluamide insect repellents reported to the AAPCC 1993-1997. Int J Toxicol 21(5):341-352
242. Zwaveling JH, et al. 1987. Exposure of the skin to methyl bromide: a study of six cases occupationally exposed to high concentrations during fumigation. Hum Toxicol 6(6):491-495.
243. Hezemans-B M, et al. 1988. Skin lesions due to exposure to methyl bromide. Arch Derm 124(6):917-921.
244.Herzstein J, et al. 1990. Methyl bromide intoxication in four field-workers during removal of soil fumigation sheets. Am J Ind Med 17:321-326.
245. Acuna MC, et al. 1997. [Assessment of neurotoxic effects of methyl bromide in exposed workers]. Rev Med Chil 125(1):36-42.
246. Hustinx WNM, et al. 1993. Systemic effects of inhalational methyl bromide poisoning: a study of nine cases occupationally exposed due to inadvertent spread during fumigation. Br J Ind Med 50(2):155-159.
247. Audry D, et al. 1985. [Rare cause of myoclonus with giant SEP's: methyl bromide poisoning. Apropos of a case with unilateral predominance]. Rev Electroenceph Neurophysiol Clin 15(1):45-52
248. Goulon M, et al. 1975. [Methyl bromide poisoning. 3 cases, 1 fatal. Neruopathological study of one case of coma with myoclonus followed for 5 years]. Rev Neurol (Paris) 131(7):445-468.
249. Hauw JJ, et al. 1986. Postmortem studies on posthypoxic and post-methyl bromide intoxication: case reports. Adv Neurol 43:201-214.
250. Mellerio F, et al. 1982. [Myoclonus of toxic origin]. Rev Electroencephalogr Neurophysiol Clin 12(3):210-218.
251. Prockop LD, et al. 1986. Seizures and action myoclonus after occupational exposure to methyl bromide. J Florida Med Ass 73:690-691
252. Mazzini L, et al. 1992. Methyl bromide intoxication: a case report. Schweiz Arch Neurol Psychiatr 143(1):75-80.
253. Moosa MR, et al. 1994. Treatment of methyl bromide poisoning with haemodialysis. Postgrad Med J 70(828):733-735.
254. Reidy TJ, Cone JE. 1994. Neuropsychological sequelae of methyl bromide: a case study. Brain Injury 8(1):83-93.
255. Uncini A, et al. 1990. Methyl bromide myoclonus: an electrophysiological study. Acta Neurol Scand 81(2):159-164.
256. Deschamps FJ, et al. 1996. Methyl bromide intoxication during grain store fumigation. Occ Med 46(1):89-90.
257. Fuortes LJ. 1992. A case of fatal methyl bromide poisoning. Vet Hum Toxicol 34(3):240-241.
258. Centers Disease Control. 1994. Deaths associated with exposure to fumigants in railroad cars--United States. MMWR 43(27):489-491.
259. Marraccini JV, et al. 1983. Death and injury caused by methyl bromide, an insecticide fumigant. J Forensic Sci 28(3):601-607.
260. Horowitz BZ, et al. 1998. An unusual exposure to methyl bromide leading to fatality. J Toxicol Clin Toxicol 36(4):353-357.
261. Langard S, et al. 1996. Fatal accident resulting from methyl bromide poisoning after fumigation of a neighbouring house; leakage through sewage pipes. J Appl Toxicol 16(5):445-448.
262. Muller M, et al. 1999. Photometric determination of human serum bromide levels--a convenient biomonitoring parameter for methyl bromide exposure. Toxicol Lett 107(1-3):155-159.

263. Taxay EP. 1966. Vikane inhalation. J Occ Med 8(8):425-426.
264. Centers Disease Control. 1987. Fatalities resulting from sulfuryl fluoride exposure after home fumigation--Virginia. MM R 36:602-604, 609-611.
265. Aghanwa HS. 2001. Attempted suicide by drug overdose and by poison-ingestion methods seen at the main general hospital in the Fiji islands: a comparative study. Gen Hosp Psychiatry 23(5):266-271.
266. Casey P, et al. 1994. Deaths from pesticide poisoning in England and Wales: 1945-1989. Hum Exp Toxicol 13(2):95-101.
267. Chan TY, et al. 1996. An estimate of the incidence of pesticide poisoning in Hong Kong. Vet Hum Toxicol 38(5):362-364.
268. Christakis-Hampsas M, et al. 1998. Acute poisonings and sudden deaths in Crete: a five-year review (1991-1996). Vet Hum Toxicol 40(4):228-230.
269. Dalvie MA, et al. 1999. Long-term respiratory health effects of the herbicide, paraquat, among workers in the Western Cape. Occ Env Med 56(6):391-396.
270. Hettiarachchi J, et al.. 1989. Self-poisoning in Sri Lanka: factors determining the choice of the poisoning agents. Hum Toxicol 8:507-510.
271. Hutchinson G, et al. 1999. High rates of paraquat-induced suicide in southern Trinidad. Suicide Life Threat Behav 29(2):186-191.
272. Klein-Schwartz W, et al. 1997. Agricultural and horticultural chemical poisonings: mortality and morbidity in the U.S.. Ann Emer Med 29(2):232-238.
273. Thompson JP, et al. 1995. Deaths from pesticide poisoning in England and Wales 1990-1991. Hum Exp Toxicol 14(5):437-445.
274. VanderHoek W, et al. 1998. Pesticide poisoning: a major health problem in Sri Lanka. Soc Sci Med; 46(4-5):495-504.
275. Fitzgerald GR, et al. 1978. Paraquat poisoning in agricultural workers. J Irish Med Assoc 71:336-342.
276. Garnier R, et al. 1994. Paraquat poisoning by skin absorption: report of two cases. Vet Hum Toxicol 36(4):313-315.
277. Newhouse M, et al. 1978. Percutaneous paraquat absorption. Arch Dermatol. 114(10):1516-1519.
278. Papiris SA, et al. 1995. Pulmonary damage due to paraquat poisoning through skin absorption. Respiration 62(2):101-103.
279. Waight JJJ, et al. 1979. Fatal percutaneous paraquat poisoning. JAMA 242(5):472.
280. Wesseling C, et al. 1997. Unintentional fatal paraquat poisonings among agricultural workers in Costa Rica. Am J Ind Med 32(5):433-441.
281. Apol AG, et al. 1976. HHE Determination Report No. HHE-75-Thiram-352, , 64 pages. Hazard Evaluation Services Branch, NIOSH, Cincinnati, Ohio.
282. Axon EJ, et al. 1995. A comparison of some of the characteristics of patients with occupational and non-occupational asthma. Occ Med 45(2):109-111.
283. Hoppin JA, et al. 2002. Chemical predictors of wheeze among farmer pesticide applicators in the Agricultural Health Study. Am J Resp Crit Care Med 165(5):683-689.
284. Honda I, et al. 1992. Occupational asthma induced by the fungicide tetrachloroisophthalo-nitrile. Thorax 479:760-761.
285. Zhang LX, et al. 2002. Occupational and environmental risk factors for respiratory symptoms in rural Beijing, China. Eur Resp J 20(6):1525-1531.
286. O'Malley M. 1997. Clinical evaluation of pesticide exposure and poisonings. Lancet 349(9059):1161-1166.
287. Jones SM, et al. 2003. Occupational asthma symptoms and respiratory function among aerial pesticide applicators. Am J Ind Med 43(4):407-417.
288. Kossmann S, et al. 1999. [Bronchia l hyperreactivity in chemical plant workers employed in the production of dust pesticides]. Wiad Lek 52(1-2):25-29.
289. Royce S, et al. 1993. Occupational asthma in a pesticides manufacturing worker. Chest 103(1):295-296.
290. Draper A, et al. 2003. Occupational asthma from fungicides fluazinam and chlorothalonil. Occ Env Med 60:76–77.
291. Vandenplas O, et al. 2000. Asthma and tetramethrin. Allergy 55(4):417-418.
292. Beard J, et al. 2003. Health impacts of pesticide exposure in a cohort of outdoor workers. Env Health Persp 111(5):724-730.
293. Montanaro A. 1992. Occupational asthma due to inhalation of antibiotics and other drugs. In: Bardana EJJr. (Ed). Occupational Asthma [pp 205-211]. Hanley and Belfus, Inc. Philadelphia
294. Deschamps D, et al. 1994. Persistent asthma after acute inhalation of organophosphate insecticide. Lancet 344:1712.
295. Blomqvist AM, et al. 1991. Atopic allergy to chloramine-T and the demonstration of specific IgE antibodies by the radioallergosorbent test. Int Arch Occ Env Health 63(5):363-365.
296. Kujala VM, et al. 1995. Occupational asthma due to chloramine-T solution. Res Med 89(10):693-695.
297. Bourne MS, et al. 1979. Asthma due to industrial use of chloramine. Br Med J 2(6181):10-12.
298. Deschamps D, et al. 1992. Persistent asthma after accidental exposure to ethylene oxide. Br J Ind Med 49(7):523-525.
299. Dugue P, et al. 1991. [Occupational asthma provoked by ethylene oxide in a nurse]. Presse Med 20(30):1455.
300. Verraes S, et al. 1995. Occupational asthma induced by ethylene oxide. Lancet 346(8987):1434-1435.
301. Savonius B, et al. 1994. Occupational asthma caused by ethanolamines. Allergy 49(10):877-881.
302. Shelton D, et al. 1992. Occupational asthma induced by a carpet fungicide—tributyl tin oxide. J Aller Clin Immunol 90(2):274-275.
303. Radon K, et al. 2001. Respiratory symptoms in European animal farmers. Eur Resp J 17(4):747-754.
304.Culver CA, et al. 1988. Probable anaphylactoid reaction to a pyrethrin pediculicide shampoo. Clin. Pharm 7:846-849.
305. Ellenhorn MJ, et al. 1997. Case report - pyrethrin death. Ellenhorn's Medical Toxicology: 2nd ed. Baltimore, MD: Williams and Wilkins, p 1626.
306. Wax PM, et al. 1994. Fatality associated with inhalation of a pyrethrin shampoo. J Toxicol Clin Toxicol 32(4):457-460.
307. Newton JG, et al. 1983. Asthmatic reactions to a commonly used aerosol insect killer. Med J Aust 1(8):378-380.
308. Salome CM, et al. 2000. The effect of insecticide aerosols on lung function, airway responsiveness and symptoms in asthmatic subjects. Eur Resp J 16(1):38-43.
309. Nriagu J, et al. 1999. Prevalence of asthma and respiratory symptoms in south-central Durban, South Africa. Eur J Epid 15(8):747-755.
310. Weiner BP, et al.1969. Insecticides, household use and respiratory impairment. Hawaii Med J 28:283-285.
311. Burns MJ, et al.1997. Another hot tub hazard. Toxicity secondary to bromine and hydrobromic acid exposure. Chest 111(3):816-869.
312. Bjorkner B. 1980. Contact urticaria and asthma from denatonium benzoate (Bitrex). Cont Derm 6(7):466-471.
313. Cone JE, et al. 1994. Persistent respiratory health effects after a metam sodium pesticide spill. Chest106(2):500-508.
314. Petrie K, et al. 2003. Symptom complaints following aerial spraying with biological insecticide Foray 48B. N Z Med J 116(1170):354.
315. Thickett KM, et al. 2002. Occupational asthma caused by chloramines in indoor swimming-pool air. Eur Res J 19(5):827-832.
316. Hery M, et al. 1995. Exposure to chloramines in the atmosphere of indoor swimming pools. Ann Occ Hyg 39(4):427-439.
317. Massin N, et al. 1998. Respiratory symptoms and bronchial responsiveness in lifeguards exposed to nitrogen trichloride in indoor swimming pools. Occ Env Med 55(4):258-263.
318. Helenius IJ, et al. 1998. Respiratory symptoms, bronchial responsiveness, and cellular characteristics of induced sputum in elite swimmers. Allergy 53(4):346-352.

Chapter 4
Children and Pesticides

Introduction

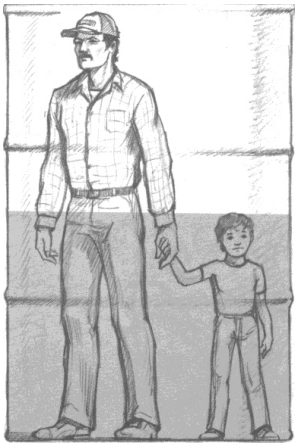
Children are not mini-adults. Under similar conditions of exposure, they respond differently to toxic chemicals. Children have more skin surface for their size; because of this larger surface-to-volume ratio, their metabolic rate is higher, and their oxygen consumption greater – 7 ml/kg body weight/min compared to 3.5 ml/kg for adults. Their respiratory rate is higher, which allows more particles to deposit into their upper and lower air passages Their immune systems are less mature, and they differ from adults in pathways of absorption, tissue distribution, and the ability to biotransform and eliminate chemicals [1,2,3 4].

During the fetal stage, a major pathway of absorption is the placenta. Most pesticides readily cross the placenta and can affect the developing child[5]. Fetal skin lacks keratin, the protective layer which is a major barrier to xenobiotic penetration. Newborn skin is highly absorptive since keratinization occurs over the three to five days following birth. Serious poisonings and deaths have occurred in newborn infants from percutaneous absorption of xenobiotics, including hexachlorophene[6], and diapers washed in a sodium pentachlorophenate solution[7]. Kidney function at birth is a fraction of normal, and glomerular filtration gradually increases to adult levels by about one year of age. Newborns do not concentrate urine at levels similar to adults until about 16 months of age[8].

Exposure

Children's exposure to pesticides includes not only residues in foods they regularly eat and drink, but often more importantly, to pesticide used in the home, lawn, or garden, or products applied directly to them such as lice treatments, and insect repellents. There are additional exposures at day care, schools, playgrounds, parks, swimming pools, and other locations.

Pesticides applied inside the home contaminate carpets, sofas, mattresses, and other household furnishings. Pesticide applied outside can be tracked in and incorporated into house dust. Both are a major source of exposure to infants and toddlers, who ingest particles adhering to food, surfaces in the home, and the skin, as well as absorption through the skin.



Vincent Perez/Artist

Under similar conditions of exposure children will absorb more than adults.

Farm worker children have additional exposures from the pesticide residues their parents carry home on their clothing, skin, hair, tools, and in their vehicles. Many live in close proximity to heavily sprayed agricultural crop areas.

Infants and toddlers are frequently placed on the floor or carpet, or on grass. Therefore, they have much more exposure to pesticide residues from flea bombs, and other applications. The breathing zone for an adult is typically four to six feet above the floor. A child's breathing zone is closer to the floor. Heavier chemicals and large respirable particulates settle out within these lower zones. Air concentrations of pesticides have been found to be higher closer to the floor[9]. Using home foggers according to label directions can result in levels of pesticide exposure to children that exceed EPA standards for children, and workplace standards for adults.

Very young children indulge in extreme oral exploratory behavior where they place everything they grasp into their mouths. A study of mouthing behavior found that children two years old and younger put things into their mouths twice as much as children older than two–81 mouthing events per day versus 42 (exclusive of eating). There were no differences between boys and girls[10]. Children are also much more likely to come in contact with contaminated

surfaces because of their "job" of exploring; nor can infants remove themselves from a toxic environment.

Risk to small children (age 1-6; mean body weight 16 kg) is usually estimated using the chronic oral reference dose (RfD) and assuming a daily intake of 100 mg of house dust [11,12]. Comparison with the maximum concentrations reviewed for chlorpyrifos, DDT, and diazinon indicates that the tolerable exposure concentration in house dust might be exceeded and that chlorpyrifos especially can be considered as a potential hazard to householders.

Tables 1 and 2 summarize findings of exposure studies in farm worker children and from home and other environmental exposures respectively. Table 3 shows the results in children of the testing of the general population for background levels of pesticide residues in blood and urine. Figure 1 shows that levels are higher in children for metabolites of commonly used pesticides.

Table 1
Pesticide Exposure in Farm Children

California children 1-3 years old[13]		Maximum farm worker children	0.44 ug/m
Of 33 pesticides % detected house dust	30.3%	Maximum controls	0.10 ug/m
Diazinon farm worker homes (4)	0.7-169 ppm	Higher in younger children - trend	p = 0.060
Non-farm worker homes (3)	0.2-2.5 ppm	Higher in younger vs older siblings	p = 0.040
Overall median	1 ppm	Live less than 200 ft from orchard	Incr. p=0.036
Chlorpyrifos farm worker homes (3)	0.2-33 ppm	US farmworker children play areas[©] [16]	
Non-farm worker homes (2)	< 1 ppm	House dust OPs[(d)]	< lod[(e)]-17,000ppm
Overall median	< 0.5 ppm	Play area soil	< lod[(e)]- 930 ppm
All other pesticides	< 2 ppm	Household dust detection	62% samples
Diazinon, chlorpyrifos per hands	20-220 ng	Homes containing at least one OP	> 1,000 ppm
Washington children agric. sprayers[14]	Absorbed /day	Control homes, all levels	< 1000 ppm
6- to 8-week spraying season	0-36 ug/kg	All 4 OPs lower non-farm homes	p < 0.05
> USEPA chronic dietary RfD	56%	Azinphosmethyl dust found in homes	100%
> WHO ADI azinphosmethyl	19%	US Children 9 months to 6 years old[17]	Median ug/g
> Phosmet reference values	< 10%	Dust - farm children	1. 92
Phosmet single dose estimates	0 -72 ug/kg	Dust - controls	0.27 p<0.001
> EPA acute RfD azinphosmethy	26%	Urine metabolites - farm children	0.05 ug/g creat
Urine adjusted volume vs creatinine	Greater	Urine metabolites controls	.01 ug/g p=.09
> Empirically derived NOELs	No estimates	Higher in children 200 ft of orchard	p=0.01
Washington orchard applicators' chn ≤6 yrs[15]	Median ug/m	Farm children OPs on hands (10 of 61)	16.4%
DMTP[(b)] detectable in 47%	0.021	Control children on hands	0%
Controls detectable in 27%	0.005p = .015		

(a) Dialkylphosphates, metabolites of organophosphates (OPs). **(b)** DMTP = dimetylthiophosphate, OP metabolite. **[c]** 26 farm, 22 farm worker, 11 non-farm families within 200 feet apple/pear orchard; non-farm ¼ mile or more.away.**(d)** Limit of detection,the smallest amount that can be found by the method used. **(e)** Organophosphates: azinphosmethyl, chlorpyrifos, parathion, phosmet.

Table 2
Pesticide Exposure in Children - Home, Other Non-Occupational

Canada boric acid (H_3BO_3) on toys[18]		
Pediatric LOAEL[(a)]		300 mg/kg bwt
MTD[(b)]		3 mg/kg bwt
MAC[©]		9.1 mg/kg toy
Italy children 6-7 yrs DAPs[(d)] urine[19]		geo. mean nmol/g cr
DMP detected in 96%		117 (7.4-1,472)
DMTP detected in 94%		104 (4-1,526)
DMDTP detected in 34%		14 (3.3-755)
DEP detected in 75%		33 (5.1-360)
DETP detected in 48%		16 (3.1-285)
DEDTP detected in 12%		7.7 (2.3-140)
Compared to adult levels		Signif. higher
UK chlorpyrifos home rx % NOEL[(e)20]		0.26-2.1%
US Arkansas children's urine[21]		Median
2,5-dichlorophenol[(f)] in 96%		9 ppb
Pentachlorophenol in 100%		14 ppb
2,4,5-trichlorophenol		1 ppb
Chlor. phenols, phenoxy herb.		LOD[(g)] 1 ppb
6 pesticides samples detected		> 10%
3 dichlorophenols detected		27%
2,4-D samples detected		20%
US Calif. Chlorpyrifos[(m)] in urine[22]	>	in parents
Chlorpyrifos infants/small chn[23]		0.0005 mg/kg/d
Cumulative OPs children		0.003 mg/kg/d
US MN[(h)] urine metabolites[24,25,26]		Pop. mean ug/l
Carbamates (1-Napthol)		3.9 (2.5-5.3)
Compared to adult levels		Lower
Malathion (MDA)		1.7 (1.1- 2.3)
Chlorpyrifos (3,5,6-TCPy)		9.6 (7.8-11)
Compared to adult levels		Much higher
Urban areas		7.2
Nonurban areas		4.7 p = 0.036
US MN[(h)] Dursban 3-7 hrs post appl.[27]		
Infant breathing zone/no ventilat.		94 ug/m^3
Infant zone ventilated room		61 ug/m^3
Infant dose[(l)] day of appl.		0.08-0.16 mg/kg
Day following application		0.04-0.06 mg/kg
US National homeowner use[28]		
Diazinon indoor inhalation		0.5 ug/kg/day
Chlorpyrifos outside perimeter		0.05 ug/kg/day
Ingestion carpet dust		0.01 ug/kg/day
Infant mouthing contribution		1-1.5 ug/kg/day
Estimates for chlorpyrifos		> EPA RfD[(j)]
Estimates for diazinon		< EPA RfD[(j)]
US National lawn-applied herbicides[29]		
Track-in by children, shoes		37x >
US Nat. PCP[(g)] log home chn v adts[30]		1.8 x > sig.
US Nat. chlorpyrifos infants,children[31]		0.0005 mg/kg-d
Cumulative organophosphates		0.003 mg/kg-d
US NC day care centers[32]		
Inhalation rates		8.3 m^3/day
Soil ingestion children 3-5 years		Lowest %
Oral dose - playing with toy		61%
Potential acute dose		356 ug/kg/day
US NJ Dursban toy dose 3-6 yrs-old[33]		208 ug/kg/day
Inhalation exposure		Negligible
Dermal dose		39%
US Texas 1% lindane treatment[34,35]		
Detected in blood after application		2-48 hours
Weight, surface area		Inversely related
Quantity of lindane applied.		Indep. related
US Texas home use chn 6 —5 yrs[36]		
Indoor air 9 homes detections		100%
Carpet dust amount / level		Highest found
23 of the 30 target pesticides[(l)]		Detected
US Seattle children 2-5 yr[37]		mean ug/mol/L
No garden use		0.09 p=.0.05
DETP[(d)] garden use		0.04
DETP[(d)] no garden use		0.03 p=0.02
At least one DAP[(d)] found		99%
DMTP and DETP[(d)]		70-75%
Pet, indoor residential use		No sig diff
Season, sex, age, income		No sig diff
DMTP[(d)] entire cohort		0.11 ug/mol/L
DETP[(d)] entire cohort		0.04 ug/mol/L
DMTP[(d)] garden use		0.19 ug/mol/L

(a) No Observable Effect Level for decreased plasma cholinest-erase (marker of organophosphate exposure). **(b)** Maximum tolerated dose. **[c]** Maximum allowable concentration. **(d)** Dialkylphosphates (see Appendix C). **(e)** No observable effect level. **(f)** Metabolite of para-dichlorobenzene, the active ingredient in moth balls, many consumer products. **(g)** Limit of detection, the smallest amount that can be found by the method used **(h)** MCPES: Miinnesota Children's Pesticide Exposure Study: probability-based sample 102 children 3-13 summer of 1997, 1-3 per urine samples per child. **(l)** 1.2 to -5.2 times the human NOEL. **(j)** Reference dose. **(k)** Pentachlorophenol, a wood preservative. **(l)** Most frequently detected Chlordane, chlorpyrifos, dieldrin, hepatachlor, pentachlorophenol. **(m)** Application by fogger, broadcast spray, crack-and-crevice treatment.

Table 3
Pesticide Residues in Blood and Urine - Children
Geometric Mean by Age
Source: National Health and Nutrition Examination Survey (NHANES) 1999-2000[38]

Chemical	Units	All ages	Age 6-11	Age 12-19
DMTP Metabolite of organophosphate pesticides	ug/g creat.	1.64	2.95	1.71
DEPMetabolite of organophosphate pesticides	ug/g creat.	0.924	1.43	0.818
3,5,6-TCPy trichloropyridinol chlorpyrifos (Dursban) metabolite	ug/g creat.	1.58	3.11	1.6
beta-HCH beta-Hexachlorcyclohexane isomer in lindane	ng/g lipid	15.0	NC*	NC*
p.p'-DDE metabolite of DDT	ng/g lipid	260	NC*	118
T**NA** trans-Nonachlor a metabolite of chlordane	ng/g lipid	18.3	NC*	NC*
2,4-6 TCP trichlorophenol [(a)]	ug/g creat.	2.54	4.82	2.4
1-Naphthol metabolite of carbaryl (Sevin)	ug/g creat.	1.52	NC*	1.04
2-Naphthol metabolite of naphthalene [(b)]	ug/g creat.	0.421	NC*	0.285
2,5-DCP 2,5-dichlorophenol , metabolite of PDB [c]	ug/g creat.	5.38	8.17	3.95
OPP ortho-phenylphenol fungicide and disinfectant	ug/g creat.	0.441	0.547	0.342

* NC = Not calculated. Proportion of results <limit of detection was too high to provide a valid result.
(a) A metabolite of several pesticides including lindane and hexachlorobenzene. **(b)** Other sources of this metabolite include tobacco smoke, and certain pollyaromatic hydrocarbons. **[c]** Paradichlorobenzene (mothballs). PDB is also used in many other consumer products.

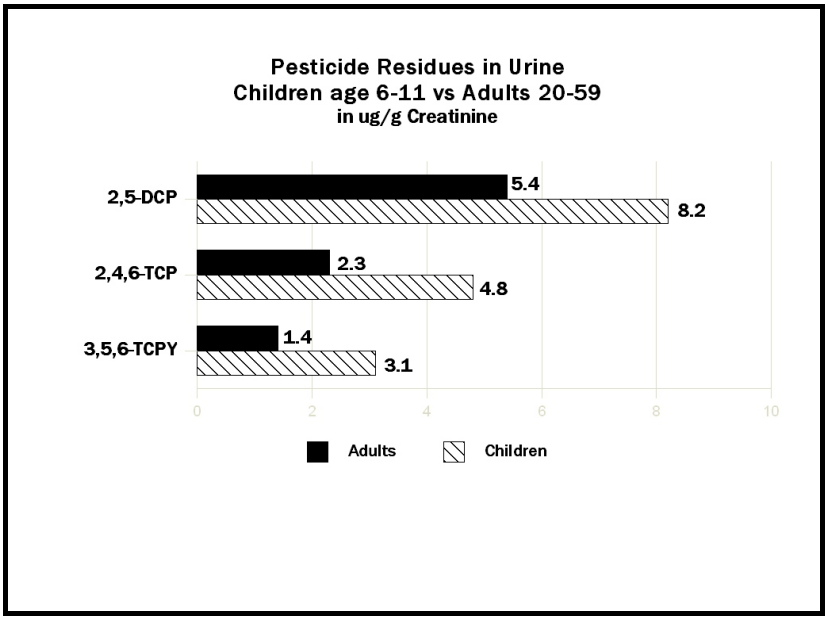


Figure 2. 2,5-DCP (2,5-dichlorophenol, metabolite of paradichlorobenzene active ingredient in mothballs). **2,4,-TCP** (2,4-trichlorophenol, a metabolite of several pesticides including hexachloro-benzene and lindane). **3,5,6-TCPy** (3,5,6-trichloropyridinol, a metabolite of chlorpyrifos.

Acute Poisoning

Deaths from pesticide poisoning in children have declined significantly in the U.S. since the 1950s. In California from 1951-1965, 128 deaths were attributed to poisoning from pesticides and other agricultural chemicals, of which 76 (59.4%) were children[39]. In North Carolina rom 1990 to 1993, 29% of the hospitalizations for pesticide poisoning were children; in South Carolina from 1971 to 1996, 28% to 37% were children. Most poisonings occur in toddlers about one year of age. Pesticide-related fatalities in children have steadily decreased for the last 20 years[40].

Organophosphate and N-methyl carbamate poisoning

Several infant poisonings from the organophosphate diazinon have been reported. A 12-week-old infant girl developed persistent hypertonicity of the extremities. Not until she was eight months old was it discovered that five weeks prior to the onset of symptoms, her home had been treated with an excessive application of diazinon. Six months after application diazinon residue remaining on the floor was 230 ng/cm^2, compared to 38 ng/cm^2 expected immediately after a normal application. Vacuum cleaner dust contained 1,700 parts per million of diazinon, and the air contained 2.8 ng/m^3. The infant's urine contained 60 parts per billion of the diazinon metabolite diethylphosphate, and 20 parts per billion of diethylthiophosphate for a dose of approximately 0.02 mg/kg/d of diazinon. When the infant was removed from the home, muscle tone returned to normal shortly thereafter[41].

Three week old twins were hospitalized with progressive respiratory distress which started about eight hours before. One twin was cyanotic, both were afebrile but had rapid, shallow breathing, profuse nasal and bronchial secretions and pinpoint pupils. They were treated with atropine and discharged after five days. The home had been sprayed by a licensed exterminator with a 1% diazinon solution for cockroach control on the morning of the day before the twins were hospitalized. The mother and three other children were out of the premises most of the day and remained well. The twins' immobility and age made them more vulnerable[42].

Transient bilateral vocal cord paralysis was reported in a three year old child who accidentally swallowed chlorpyrifos[43]. A poisoning with the organophosphate demeton-S-methyl was reported recently in a two year old[44]. Several cases of amitraz poisoning were reported in children from 2-1/2 to 6 years old , 30 to ninety minutes after accidental ingestion of an improperly stored liquid pesticide. Signs and symptoms were unconsciousness and drowsiness in all cases, myosis in 84% bradycardia in 45%, respiratory insufficiency 27%, and hypotension in 18%. All responded to treatment with atropine within eight to 14 hours and were discharged within 48 hours[45,46]. There are also other reports of amitraz poisoning in children[47],[48]

Caksen H, Odabas, D, Arslan S, et al. 2003. Report of eight children with amitraz intoxication. Hum Exp Toxicol 22(2):95-97.

Yüzüncü Yil Univ, Faculty of Medicine, Dept of Pediatrics, 65300, Van, Turkey. huseyincaksen@hotmail.com

ABSTRACT: Many pesticides are formulated in organic solvents. An example is amitraz, one of the formamidine groups of pesticidal chemicals. It is commonly used for the treatment of generalized demodicosis in dogs and for the control of ticks and mites in cattle and sheep. In this article, the clinical and laboratory findings of eight children with amitraz intoxication are reviewed. The purpose was to enlighten the findings of amitraz intoxication in children. Of the eight patients, five (62.5%) were boys, three (37.5%) were girls, and the ages ranged from 1 to 4 years. All children accidentally ingested amitraz orally, with no dermal exposure. The most common observed signs were decreased consciousness and bradycardia. Leukocytosis, hyperglycemia, hypernatremia, increased serum aspartate transaminase level, and prolonged partial prothrombin time were diagnosed in children. None of the children had hypothermia, hypotension, or convulsion and none of the patients died. The findings show that the initial signs and symptoms of acute amitraz intoxication appeared severe but they disappeared, with only supportive care needed in most cases within a few days.

A report of pesticide poisoning in 37 infants and children, found that 76% were poisoned by ingesting an improperly stored liquid pesticide, and 14% after playing on carpets and floors of homes that had been sprayed or fogged by unlicensed exterminators. The most common signs and symptoms were miosis (73%), excessive salivation (70%), muscle weakness (68%), lethargy (54%) and tachycardia (49%), Seizures developed in 22%, and 38% required endotracheal intubation and mechanical ventilation. They responded to treatment with atropine and/or pralidoxime, and there were no deaths. Pneumonitis and/or atelectasis developed in ten patients, including six who had ingested a

petroleum distillate-containing insecticide[49].

Of 36 children and 24 adults who ingested rat poison containing methomyl or aldicarb, the children's signs and symptoms differed significantly from adults, although serum cholinesterase depression was similar. The predominant symptoms in young children were central nervous system depression and hypotonia. The most common muscarinic effect was diarrhea. In adults, the main signs were miosis and fasciculations, which were less frequent in children. Central nervous system depression, hypotonia, and diarrhea were uncommon in adults[50]. The clinical presentation of carbamate and organophosphate poisoning in early childhood and response to therapy differs from those of adults and older children[51].

A review of 5,541 children admitted to pediatric intensive care of a university hospital from 1990 to 2000, found 54 (1%) with cholinesterase inhibitor insecticide poisoning. Complications included coma (31%), seizures (30%), shock (9%), arrhythmias (9%), and respiratory failure requiring ventilation (35%). No significant differences were found in the incidence of seizures, cardiac arrhythmias, respiratory failure, mortality, duration of ventilation, or PICU stay, according to route of exposure, or state of decontamination. Four children died (7%). Mortality was associated with the presence of a cardiac arrhythmia (likelihood ratio 8.3) and respiratory failure (likelihood ratio 3.3)[52].

Acute pancreatitis was found in five children in a prospective study of 17 consecutive children with typical organophosphate and carbamate poisoning. They had significantly elevated serum levels of both immunoreactive trypsin, amylase, and glucose compared to other patients and controls. None had hypocalcemia, renal dysfunction, or acidosis, and all recovered completely[53].

Sood A, Midha V, Sood N. 2003. Gastric outlet obstruction as a late complication of ingestion of diazinon. Indian J Gastroenterol 22(3):106-107.
Department of Medicine, Dayanand Medical College and Hospital, Ludhiana. ajitsood10@sify.com

ABSTRACT: Acute gastrointestinal symptoms are known to occur with organophosphorus compounds poisoning. Delayed complication in the form of gastric outlet obstruction has not been reported to date. We report gastric outlet obstruction developing after diazinon ingestion in a young girl. She responded to endoscopic balloon dilatation.

Permethrin poisoning
Permethrin is considered to have a low potential for poisoning. Severe permethrin toxicity was reported in three siblings aged 9, 7 and 19 months treated for head lice with a 1.0% permethrin cream rinse. The children's bedding was then saturated with 3 canisters of 0.5% permethrin spray, and two pounds of 0.25% permethrin powder was sprinkled throughout the home. Over the next 3 days all five family members developed mild diarrhea and emesis. The 19-month female developed progressive gastrointestinal symptoms and cough attributed to an infection. On day four she presented with agitation, ataxia, seizures, fasiculations, cardiac conduction blockade, and respiratory failure due to severe pulmonary edema. An infectious disease work-up was negative, and the permethrin exposure was elucidated the day of ICU admission. Surface swab testing of the family's home for permethrin revealed 2.4 ppm in the parent's bedroom, 277 ppm in the child's upholstered chair, 15.3 ppm in the family room carpet, 70.9 ppm in the child's bedroom carpet, 9.7 ppm in the child's toys, and 2 ppm in the kitchen. Only mild effects were noted in two adults and two older siblings[54].

Lindane poisoning
There is a recent report of poisoning in toddlers from accidental ingestion of lindane, in which a 17- month-old girl suffered a single seizure. A 3-year-old boy was listless, nauseated, pale, and had decreased responsiveness to verbal and tactile stimulation. A 4-year-old girl became nauseated and required bag-valve-mask ventilation for hypoventilation. All three recovered without apparent sequelae[55]. A follow-up study of 41 children less than five years old, acutely poisoned by lindane ingestion, found one child with a persistent seizure disorder[56].

Boric acid poisoning
Boric acid solution was inadvertently used to dilute concentrated formula and fed to 24 day old and 14 month old siblings, who developed irritability, diarrhea, and perineal erythema in the 24 day old. The 24 day old was treated with peritoneal dialysis, both recovered completely without sequelae. The total amount ingested was 2.6 g in the 24

day old (peak level 146 ug/ml), and 1.95 g in the 14 month old (peak levels 56 ug/ml)[57].

Other pesticide poisonings

Poisoning with the phenoxy herbicide MCPA in a three month old child successfully treated with plasmapharesis was reported[58]. Most cases of paraquat poisoning and deaths in children are from accidental ingestion[59,60,61,62,63]. Homicide by paraquat was reported in two children who presented with gastrointestinal ulceration and acute respiratory distress, and pneumomediastinitis. Bullous emphysema was a common autopsy finding [64]. Attempted homicide with the herbicide imazapyr (Arsenal) involving a child was also reported[65]. Illegal pesticides continue to be a source of poisoning of children[66,67].

Report from Iran show that most non-occupational pesticides poisonings are in children less than six, and more boys are poisoned than girls[68]. In Costa Rica children less than five accounted for 39.2% pesticide poisoning cases in 1997, and the prevalence was the same in boys and girls[69].

Barrueto F Jr, Furdyna PM, Hoffman RS, et al. 2003. Status epilepticus from an illegally imported Chinese rodenticide: "tetramine". J Toxicol Clin Toxicol 41(7):991-994.

New York City Dept of Health and Mental Hygiene, NY City Poison Control Center, New York, NY 10016. fbarr001@umaryland.edu

ABSTRACT: INTRODUCTION: The following case report demonstrates the severe consequences of refractory convulsive status epilepticus from an unfamiliar imported toxin, tetramethylenedisulfotetramine (TETS), and the difficulties of identifying the offending agent.

CASE REPORT: A previously healthy 15-month-old girl was found by her parents playing with a white rodenticide powder brought from China. Fifteen minutes later, the child developed generalized seizures and was brought to an Emergency Department (ED). Her initial fingerstick blood glucose was 108 mg/dL. In the ED, the child was intubated for status epilepticus. Despite aggressive therapy with lorazepam, phenobarbital, and pyridoxine, she had 4 h of intermittent generalized seizure activity. She was extubated on the third hospital day, but appeared to have absence seizures and cortical blindness. Continuous electroencephalogram monitoring, performed weeks later, revealed severe diffuse cerebral dysfunction with multiple epileptogenic foci. The child remains developmentally delayed and is on valproic acid therapy for seizure control. Translation of the Chinese package labeling did not clarify its contents. Tetramethylenedisulfotetramine was finally confirmed by gas chromatography-mass spectrometry (GC-MS) in this rodenticide product and then quantified against a TETS standard that was synthesized in our laboratory.

CONCLUSION: Tetramethylenedisulfotetramine is grouped with other "cage convulsants," such as picrotoxin, since they have a similar intercalating cyclical molecular structure and cause seizures through non-competitive gamma-aminobutyric acid (GABA) antagonism. The oral lethal dose 50% (LD50) in humans is estimated to be as low as 100 microg/kg. Our patient has severe diffuse cerebral dysfunction likely secondary to prolonged seizure activity after exposure to TETS.

Poisoning in working children

There are almost no data on pesticide poisoning in working children. A survey of eight states and poison control centers found 531 youths with acute occupational pesticide-related illnesses. Most were related to insecticides (68%), and most were of minor severity (79%). The average annual incidence rate among youths aged 15 to 17 years was 20.4 per billion hours worked, and the incidence rate ratio among youths compared to adults was 1.71 (1.53, 1.91)[70]. A study of pesticide signs and symptoms among farmers' families in five agricultural communities in rural El Salvador, found detectable levels of organophosphate metabolites in nearly half of 358 samples, 30% in those who did not work in agriculture. The levels were similar for children and adults[71].

Deet poisoning (N-N-diethyltoluamide, OFF!, Skintastic)

It is estimated that deet is used on 23-29% of children annually in the U.S[72]. A poison control study of deet related calls found that the greatest number of reported exposures involved infants and children, but this group experienced lower rates of adverse effects than teens or adults[73]

Deet is very toxic to the brain and nervous system. Signs and symptoms of mild poisoning include headache,

restlessness, irritability, crying spells and other changes in behavior. In more severe poisoning there can be slurring of speech, tremor (shakiness), convulsions, and coma. Deet has caused death in children from absorption through the skin when it was applied repeatedly and/or in a high concentration. There is a report of a five year old child at a day camp who had a major seizure (convulsion) without any other symptoms shortly after deet was applied to his skin.

A review of 17 cases of toxic encephalopathy in children (56% girls) found it occurred not only after ingestion or repeated and extensive application, but also from brief exposure to a product containing 45% deet. Of the skin application cases, 33% were in a product containing less than 20%t. The review described a case in an 18-month-old boy following brief exposure to 17.6% deet[74].

Four healthy boys three to seven years old, who had never had a seizure or neurologic problem, developed seizures eight to 48 hours after three or less applications of deet at a summer camp. One boy who had a rash before his seizure developed a rash to the dilantin medication used to control the seizures[75]. A five year old girl, sprayed with deet nightly for three months, developed headaches and slurred speech, progressing to staggering gait, shaking, screaming, and seizures, and episodes of stiffening into sitting position, extending extremities, flexing fingers and dorsiflexing toes. She died 24 days later. At autopsy the brain showed generalized edema with intense congestion of meninges. The same author reported another case in an 18 month old who ingested an unknown amount of liquid deet. She displayed extreme irritability and bizarre movements, but her condition improved steadily [76].

A 5-year-old boy with mild developmental delay , experienced a major motor seizure at day camp after topical application that morning and later in the day of deet. His seizures continued in the emergency room and were eventually brought under control with diazepam[77]. A case report of seizures and coma which developed in a child two hours after accidental ingestion of a low dose of deet. (80 mg/kg). He recovered without sequelae[78] Seizures and acute behavior change developed in an 8-year-old girl following exposure to deet, with recover in three days after anticonvulsant medication[79]. A one year old child died after development of seizures and coma one hour after accidental ingestion of a large amount of concentrated deet[80].A case was reported of a four year old boy with mental retardation, impaired sensorimotor coordination, and craniofacial dysmorphology, whose mother applied deet daily throughout her pregnancy, in addition to taking the anti-malaria drug chloroquine prophylactically[81].

A Reye-like syndrome was reported in a 6 year old girl with extensive exposure to deet who was deficient in ornithine carbamoyl transferase (OCT). This deficiency delayed metabolism of deet in the liver and removal from the body, increasing its toxic effect. The author suggest that other cases of deet related toxic encephalopathy might also have suffered from OCT deficiency[82].

Generalized urticaria has also been reported[83].

Asthma: Pesticide exposure, even at low levels, can trigger severe reactions among persons with asthma, especially children. However there is almost no epidemiological data on pesticide exposure as an independent risk factor for asthma in children. A fatality associated with sudden irreversible bronchospasm from a pyrethrin shampoo was reported[84].

Wheezing among Iowa farm children has been associated with herbicide exposure[85], but other studies show farmer's children to be at lower risk of allergic disease, including hay fever[86, 87].

A study in New Zealand found no adverse effects on asthmatic children from community spraying of Bacillus thuringiensis (BT)[88]. In a pesticide fire, respiratory symptoms in the affected surrounding community were highest in preschool children and asthmatics[89]

Cancer in Children: Childhood cancer, notably leukemia, brain cancer, non-Hodgkin's lymphoma, soft tissue sarcoma, and Hodgkin's disease, has been associated with pesticide exposure, often with greater relative risks than among exposed adults, suggesting greater susceptibility in children. These differences in risk may be due to developmental factors or differences in pesticide exposure.

In 1983, there were reports of "too many children with cancer" in the small agricultural town of McFarland in Kern County, California. From 1982 to 1985, when one case of cancer was expected, there were eight children with cancer: two cases of acute lymphocytic leukemia, two of soft tissue sarcoma, and one case each of Wilms' tumor, brain cancer, non-Hodgkin lymphoma, and osteosarcoma. Most were children of farm workers.

Six years later, there was a report of another cancer cluster in farm worker children in Earlimart, a town in Tulare county 14 miles north of McFarland. From 1986 to 1989, when less than 2 cases were expected, there were six children with cancer: three cases of acute lymphocytic leukemia, and one case each of Wilm's tumor, lymphoma, and soft tissue sarcoma. All were children of farm workers. Both McFarland and Earlimart were confirmed as cancer clusters by the State of California Department of Health Services.[1]

Cancer in Children	
Leukemia	30%
Brain and spinal cord	21%
Neuroblastoma	7.3%
Wilm's tumor	5.9%
Hodgkin disease	4.4%
Non-Hodgkin lymphoma	4.0%
Soft tissue sarcoma	3.4%
Retinoblastoma	2.8%
Osteosarcoma	2.7%
Ewing sarcoma	1.8%

More pesticides are used in the San Joaquin Valley where the children live, than any other area in California. pesticide use area in California. A large percentage of the pesticides used are known or suspect carcinogens (see Appendix B). Infants and young children are the most vulnerable to adverse health effects of pesticides. They can be affected by levels that are not toxicologically significant in adults. Children are less likely to have exposure to other to toxic substances such as alcohol, tobacco, and drug then adults. The amount of time between exposure and adverse chronic effects is much shorter in children. It is therefore not surprising that some of the highest pesticide related cancer risks are seen in children.

At the time of the discovery of a cancer cluster in McFarland in 1983, there were no studies of pesticide exposure as a risk factor for cancer in children. There are now many studies reporting that parent's work, home, and other exposure to pesticides, can increase the risk of cancer in their children. The types of cancer are the same as those first reported in the farm worker children.

The following discussion summarizes the findings in studies of cancer in children potentially related to pesticides. As discussed earlier, it includes only study results that were statistically significant, and some of borderline significance. Because the source and type of exposure affects risk, the summary discusses cancer in children in two categories: occupational exposure of their parents (see Tables 1,3), and home and other non-occupational exposures (see Table 2,3). The citations are in the tables.

Bone Cancer

Reported risks are higher for Ewing's sarcoma than for osteosarcoma. An 880% increase in Ewing's sarcoma was found in children if the father was a farm worker, and a 780% increase if the mother was a farm worker exposed to pesticides. A borderline significant increase was found if the father was a farmer. A 390% increase in risk of osteosarcoma was found if the parents were farmers. There are no reports of risk for home or other non-occupational exposures.

Brain Cancer

A 1,080% increase found if there was prenatal home use of pet flea/tick sprays and foggers is the highest reported. A 620% increase was found if there was home use of aerosol bombs and foggers, and increases for use of pet flea collars, termite treatment, and pest strips. A 480% increase found for Kwell (lindane) treatment of head lice was borderline significant. nother study found a smaller increase for home use of pest strips.

Leukemia

The highest reported risk is a 1,240% increase in acute non-lymphocytic leukemia (ANLL) in children whose parents

[1] (1) California DHS. 1988. Epidemiologic Study of Adverse Health Effects in Children in McFarland, California, Phase II Report. Epidemiological Studies and Surveillance Section. Berkeley, California, January 19, 1988. (2) Coye MJ, Neutra R. Investigation of the Earlimart childhood cancer cluster. California DHS Environmental Health Investigations Branch. Berkeley, California.

had prolonged exposure to pesticides at work. There are several reports of an increase in acute lymphocytic leukemia (ALL) if the mother was exposed at work. A 650% Increase in ALL was found for parents' use of home garden pesticides at least once a month, with an additional 250% increase if the mother was the user. Indoor use of pesticides more than once a week almost quadrupled the risk. A 280% increase was found for commercial home extermination during pregnancy in the first three years of life, and a 360% increased risk if the home was treated in the second year after birth.

Non-Hodgkin Lymphoma
The highest reported risk is a 1,380% increase if the mother was exposed to pesticides at work during pregnancy. Frequent home use increased risk 730%[32]. Non-Hodgkin Lymphoma is the type of cancer most frequently found in adults with pesticide exposure.

Neuroblastoma
Over 200% increased risk was found if the parents were farmers, if the parents were exposed to insecticides at work,, and for home garden use if the child was younger than one year of age[33].

Soft Tissue Sarcoma
An increase in this rare type of cancer was found if the mother was a farmer, and for home yard pesticide use[24].

Wilm's Tumor
A study in Brazil, which has one of the highest rates of Wilm's tumor in the world, found a very high risk if the parents were farmers or farm workers. A lower increase was found for commercial home extermination.

Other Cancers
A 1,000% increase in the risk of retinoblastoma was found if the maternal grandparents were farmers. Having farmer parents increased the risk of eye cancer, Hodgkin's disease, and non-seminoma testicular cancer.

Other Conditions
Sudden Infant Death Syndrome (SIDS)
A study of 34 unexplained infant deaths and 72 controls done in homes illegally sprayed with methyl parathion, found that SIDS infants were 4.6 times more likely to have lived in an illegally treated home, but the confidence interval was very wide. Methyl parathion was detected in wipe samples (>0.02 mg/100 cm^2) in five homes, three previously occupied by case infants. The authors conclude the association was not statistically significant and should be interpreted cautiously[90].

Chlorinated hydrocarbon pesticide residues (hexachlorbenzene, alpha, beta and gamma hexachlorcyclohexane, heptachlor epoxide, dieldrin, total DDT) were measured in subcutaneous fat of SIDS cases from rural and urban areas and controls. No significant differences were found[91].

An autopsy study of 54 SIDs cases and 108 controls in which tissue levels of arsenic, lead, cadmium, mercury, and pentachlorphenol were measured in several organs, found no differences between SIDS cases and controls. Nor was there a correlation between infections of the respiratory system and higher concentrations of these agents in the organs of SIDS cases[92].

Table 3
Parents' Agricultural and Other Occupational Pesticide Exposures and Increased Cancer Risk in Children
(See Appendix F for explanation of the table)

Bone Cancer	
Australia father a farmer[(a)93]	OR 3.5 bs*
Child lived on a farm	OR 1.6 bs*
Canada maternal farm pesticide exposure[(a)94]	OR 7.8
Norway farmer parents[(b)95]	RR 2.9
US California father an agricultural worker[(a)96]	OR 8.8
Father exposed pesticides, fertilizers	OR 6.1
Brain Cancer	
Europe father works in agriculture[97]	OR 2.2 bs*
France child lived on a farm[98]	OR 6.7
Germany wood preservative[99]	OR 3.28
Norway pesticide purchases[3]	RR 1.6
Parents pig farmers (all)	RR 1.59
Parents pig farmers[©)]	RR 3.11
Grain farming[©)]	OR 1.72
Grain farmers (all)	RR 1.29 bs*
Sweden parental exposure[(d)100]	OR 2.36
US maternal prenatal exposure to pigs[(e)101]	OR 11.9
Child prenatal exposure to pigs	OR 3.0
Child farm residence	OR 3.8
Maternal exposure to pigs	OR 4.0
Maternal prenatal exposure to poultry	OR 3.0
Child prenatal exposure to poultry	OR 2.2
Maternal exposure horses in pregnancy	OR 2.2 bs*
US/Canada[(f)] farm residence[(g)] > 1 year[(e)102]	OR 5.0
Eye Cancer	
Norway farmer parents[3]	OR 3.17
US/Canada[(h)] maternal grandparents farmers[103]	OR 10.0
Hodgkin Disease	
Norway farmer parents[2]	RR 2.68
Kidney Cancer	
England/Wales parental pesticide exposure[104]	PMR 1.59
Leukemia	
China pesticide exposure during pregnancy[105]	OR 3.5
Germany pest. exposure during pregnancy[106]	OR 3.6
Maternal exposure ever	OR 2.5
Paternal exposure ever	OR 1.6
Pesticide use on farms	OR 1.5 bs*
Germany maternal occupational exposure[107]	Increase
Italy farmer parents[108]	Increase
Japan prenatal parental exposure[109]	Increase
Norway parents pig farmers[3]	RR 2.10
US California propargite use area[110]	OR 1.48
US/Canada[(h)] preconceptual exposure[111]	OR 2.09
US/Canada[(h)] child less than 5 years old[(l)112]	OR 11.4
Children all ages[(l)]	OR 3.8
Father exposed more than 1,000 days	OR 2.7 bs*
Non-Hodgkin Lymphoma	
Germany exposure during pregnancy[14]	OR 11.8
Maternal pesticide exposure ever	OR 4.1
Paternal pesticide exposure ever	OR 1.9 bs*
Neuroblastoma	
Norway farmer parents[3]	RR 2.51
US New York maternal exposure insecticides[113]	OR 2.3
Paternal exposure to creosote	OR 2.1
US/Canada father a landscaper[114]	OR 2.3 bs*
Soft Tissue Sarcoma	
Italy maternal occupation as a farmer[16]	Increase
Testicular Cancer	
Norway farmer parents[3]	SIR 1.25
Fertilizer use	RR 2.44
Non-seminoma type	RR 4.21
Wilm's Tumor	
Brazil father a farm worker[115]	OR 3.24
Mother a farm worker[(j)]	OR 128
Father exposed, diagnosed age less than 2	OR 4.0
Mother exposed, diagnosed age less than 4	OR 14.8
Father exposed, boys	OR 8.56
Norway farmer parents[3]	RR 8.87

* bs = borderline significance

(a) Ewing sarcoma. **(b)** Osteosarcoma **[c]** Nervous system tumors **(d)** Non-astrocytic neuroepithelial type only **(e)** Primitive neuroectodermal **(f)** Retinoblastoma **(g)** The Children's Cancer Study Group, a collaboration between the U.S.: CO, DC, IL, IN, IA, MI, MN, NJ, NY, NC, OH, OR, PA, TN, TX, UT, WI, and Canada: BC, NS, ONT. **(h)** One year before to 3 years after birth. **(I)** Parent exposed more than 1,000 days **(j)** Based on a very small number of cases.

Table 4
Home, Garden, Pet, and other Pesticide Exposures
Increased Cancer Risk in Children
(See Appendix F for explanation of table)

Brain Cancer	
France home treatment in childhood[7]	OR 2.0 bs*
US Denver pest strip use[116]	OR 1.8[(a)]
US Los Angeles flea/tick foggers, sprays only[117]	OR 10.8
Prenatal exposure child < age 5 at diagnosis	OR 5.4
Not following label instructions	OR 3.7
Treating more than 1 pet (trend significant)	OR 3.5
Child less than age 5 at diagnosis	OR 2.5
Mother applied product, cleaned up	OR 2.2
Use of any type of pet flea/tick products	OR 1.7
US Missouri use bombs and foggers[118]	OR 6.2
Any termite treatment	OR 5.2
Pet flea collar use	OR 5.5
Pest strip use	OR 4.4
Kwell /lindane head lice treatment	OR 4.8 bs*
Garden/orchard insecticide use	OR 4.6 bs*
Garden use diazinon	OR 4.6
Garden use carbaryl	OR 3.0
Yard herbicide use	OR 2.6
US Ohio home use during pregnancy[119]	Increase
Leukemia	
England/Wales propoxur use mosquito control[120]	OR 9.7
Germany (West) home and garden use[14]	OR 2.5 bs*
US California professional extermination[(b)121]	OR 2.8[e]
Second year after birth	OR 3.6
Insecticide use during pregnancy	OR 2.1
Insecticide use 3 months prior to pregnancy	OR 1.8
US Los Angeles garden use by mother[122]	OR 9.0
Garden use once per month either parent	OR 6.5
Father's use indoors	OR 4.0
Indoor use more than once a week	OR 3.8
Mother's use indoors	OR 3.2
US Denver pest strip use[24]	OR 3.0[©)]
Pest strip use	OR 1.7[(d)]
Pest strip use	OR 2.6[(a)]
US/Canada postnatal rodenticide use[19]	OR 1.8
US St. Jude Hospital garden use[123]	OR 2.1
Non-Hodgkin Lymphoma	
Germany professional home treatment[14]	OR 2.6
US St. Jude Hospital garden use	X^2 17.2
US Denver home extermination[24]	OR 1.8[(d)]
US/Canada frequent home use[124]	OR 7.3[(e)]
Home extermination	OR 3.0
Post natal exposure	OR 2.4
Neuroblastoma	
US/Canada home garden use[125]	OR 2.2[f]
Mother applied pesticide	OR 2.2
Garden herbicide use	OR 1.9
Ant, roach product use	OR 1.8 bs*
Pesticide use in garden	OR 1.7 bs*
Pesticide use in home	OR 1.6 bs*
Soft Tissue Sarcoma	
US Denver yard pesticide use[24]	OR 3.9[(a)]
Wilm's Tumor	
US/Canada home extermination ever[126]	OR 2.16
Home extermination once a year	OR 2.41
Home extermination more than twice a year	OR 2.19

* bs = borderline significance

(a) Two years prior to diagnosis through diagnosis. **(b)** One year before to 3 years after birth. **[c]** In the last three months of pregnancy. **(d)** Birth through 2 years prior to diagnosis. **(e)** Trend significant for use on most days. **(f)** Child less than age 1 at diagnosis.

Table 5
Pesticide Exposure a nd Cancer in Children
Decreased Risk or No Associations Found
(See Appendix F for information of table)

Parental Occupational Exposure		Home, Garden, Other Exposure	
All Types of Cancer		**Brain Cancer**	
US California agricultural pesticide use[18]	OR 0.95	Australia home pesticide use[35]	No association
Brain		Germany pesticide exposure[7]	No association
Australia living on a farm[127]	Decrease	US Los Angeles head lice treatment[25]	No association
Germany parents exposed to pesticides[7]	No association	Yard and garden use	No association
Leukemia		**Leukemia**	
Canada father chlorophenate (sawmills)[128]	No association	US Denver yard treatment[24]	OR 0.9[(a)]
Sweden parental pesticide exposure[8]	No association	**Non-Hodgkin Lymphoma**	
Non-Hodgkin Lymphoma		Germany garden pesticide use[14]	OR 0.8
Germany farm pesticide use[14]	OR 0.5	**Soft Tissue Sarcoma**	
Testicular		US Denver yard treatment[24]	OR 0.8 [(b)]
Denmark parents in agriculture[129]	No association		
Child lived on a farm	No association		
Wilm's Tumor			
Germany parental pesticide exposure[7]	No association		

(a) Birth through 2 years prior to diagnosis.
(b) In the last three months of pregnancy

References:

1. Schiller-S CF, et al. 1994. Experimental data for total deposition in the respiratory tract of children. Toxicol Lett 72(1-3):137-144.
2. Bearer CF. 1995. How are children different from adults? Env Health Pers 103(Suppl 6):7-12
3. Bruckner JV, et al. 1999. Biological factors which may influence an older child's or adolescent's responses to toxic chemicals. Regul Toxicol Pharmacol 29(2 Pt 1):158-164.
4. WHO. 1986. Environmental Health Criteria 59: Principles for evaluating health risks from chemicals during infancy and early childhood:. Geneva: .
5. Schardein JL. 1993. Pesticides. Chemically Induced Birth Defects 2:675-721
6. Shuman RM, et al. 1975. Neurotoxicity of hexachlorophene in humans. II. A clinicopathological study of 46 premature infants. Arch Neurol 32(5):320-325.
7. Robson AM, et al. 1969. Pentachlorophenol poisoning in a nursery for newborn infants: I. Clinical features and treatment. J Ped 75:309-316.
8. John EG, et al. 1991. Development of renal excretion of drugs during ontogeny. In: Fetal and Neonatal Physiology, Vol 1 (Polin RA, ed). [pp 153-155] W.B. Saunders, Philadelphia.
9. Fenske RA, et al. 1991. Development of dermal and respiratory sampling procedures for human exposure to pesticides in indoor environments. J Expo Anal Env Epid 1(1):11-30.
10. Tulve NS, et al. 2002. Frequency of mouthing behavior in young children. J Expo Anal Env Epid 12(4):259-264
11. Roberts JW, et al.. 1995. Exposure of children to pollutants in house dust and indoor air. Rev Env Contam Toxicol 143:59-78.
12. Butte W, et al. 2002. Pollutants in house dust as indicators of indoor contamination. Rev Env Contam Toxicol. 175:1-46.
13. Bradman MA, et al. 1997. Pesticide exposures to children from California's Central Valley: results of a pilot study. J Expo Anal Env Epid 7(2):217-234.
14. Fenske RA, et al. 2000. Biologically based pesticide dose estimates for children in an agricultural community. Env Health Persp 108(6):515-520.
15. Loewenherz C, et al. 1997. Biological monitoring of organophosphorus pesticide exposure among children of agricultural workers in central Washington State. Env Health Persp 105(12):1344-1353.
16. Simcox NJ, et al. 1995. Pesticides in household dust and soil: exposure pathways for children of agricultural families. Env Health Persp 103(12):1126-1134.
17. Lu C, et al. 2000. Pesticide exposure of children in an agricultural community:. Env Res 84(3):290-302.
18. Craan AG, et al. 1998. Hazard assessment of boric acid in toys. Regul Toxicol Pharmacol 3:271-280.
19. Aprea C, et al. 2000. Biologic monitoring of exposure to organophosphorus pesticides in 195 Italian children. Env Health Perspect 108(6):521-525.
20. Griffin P, et al. 1999. Oral and dermal absorption of chlorpyrifos: A human volunteer study. Occ Env Med 56(1):10-13.
21. Hill RH, et al. 1989. Residues of chlorinated phenols and phenoxy acid herbicides in the urine of Arkansas children. Arch Env Contam Tox 18:469-474.
22. Krieger RI, et al. 2001. Biomonitoring of persons exposed to insecticides used in residences. Ann Occ Hyg 45(Suppl 1):S143-S153.
23. Cochran RC. 2002. Appraisal of risks from nonoccupational exposure to chlorpyrifos. Regul Toxicol Pharmacol 35(1):105-121.
24. Adgate JL, et al. 2001. Measurement of children's exposure to pesticides: analysis of urinary metabolite levels in a probability-based sample. Env Health Persp 109(6):583-590.
25. Freeman NC, et al. 2001. Quantitative analysis of children's microactivity patterns. J Expo Anal Env Epid 11(6):501-509.
26. Quackenboss JJ, et al. 2000. Design strategy for assessing multi-pathway exposure for children. J Expo Anal Env Epid 10(2):145-158.
27. Fenske RA, et al. 1990. Potential exposure and health risks of infants following indoor residential pesticide applications. Am J Public Health 80(6):689-693.
28. Lewis RG, et al. 2001. Movement and deposition of two organophosphorus pesticides within a residence after interior and exterior applications. J Air Waste Manag Assoc 51(3):339-351.
29. Lewis RG, et al. 1999. Residential indoor exposures of children to pesticides following lawn applications. GRA&I, Issue 26.
30. Cline RE, et al. 1989. Pentachlorophenol measurements in body fluids of people in log homes and workplaces. Arch Env Contam Tox 18:475-481.
31. Cochran RC. 2002. Appraisal of risks from nonoccupational exposure to chlorpyrifos. Regul Toxicol Pharmacol 35(1):105-121.
32. Wilson NK, et al. 2001. Levels of persistent organic pollutants in several child day care centers. J Expo Anal Env Epid 11(6):449-458.
33. Gurunathan S, et al. 1998. Accumulation of chlorpyrifos on residential surfaces and toys accessible to children. Env Health Perspect 106 Suppl 2:9-16.
34. Ginsburg CM, et al. 1983. Absorption of gamma benzene hexachloride following application of Kwell shampoo. Pediatr Dermatol 1(1):74-76.

35. Ginsburg, CM, et al. 1977. Absorption of lindane (gamma benzene hexachloride) in infants and children. J Pediat 91(6):998-1000.
36. Lewis RG, et al. 1994. Evaluation of methods for monitoring the potential exposure of small children to pesticides in the residential environment. Arch Env Contam Toxicol 26(1):37-46.
37. Lu C, et al. 2001. Biological monitoring survey of organophosphorus pesticide exposure among pre-school children in the Seattle metropolitan area. Env Health Persp 109(3):299-303.
38. Second National Report on Human Exposure to Environmental Chemicals, CDC National Center for Environmental Health. NCEH Pub. No. 02-0716. January 2003. http://www.cdc.gov/exposurereport/
39. West I. 1966. Pesticide-induced illness. Public health aspects of diagnosis and treatment Calif Med. 195(4):257-261.
40. Sumner D, et al.. 2000. Pediatric pesticide poisoning in the Carolinas: an evaluation of the trends and proposal to reduce the incidence. Vet Hum Toxicol 42(2):101-103.
41. Wagner SL, et al.1994. Chronic organophosphate exposure associated with transient hypertonia in an infant. Pediatrics 94(1):94-97.
42. English T,et al. . 1970. Organic phosphate poisoning--Cleveland, Ohio. MMWR 19:40, 397,404.
43. Aiuto LA, et al. 1993. Life-threatening organophosphate-induced delayed polyneuropathy in a child after accidental chlorpyrifos ingestion. J Pediat 122(4):658-660.
44. Rolfsjord LB, et al. 1998. Severe organophosphate (demeton-S-methyl) poisoning in a two-year-old child. Vet Hum Toxicol 40(4):222-224
45. Aydin K, et al. 1997. Amitraz poisoning in children: clinical and laboratory findings of eight cases. Hum Exp Toxicol(11):680-682.
46. Yaramis A, et al. 2000. Amitraz poisoning in children. Hum Exp Toxicol 19(8):431-433.
47. Kennel O, et al. 1996. Four cases of amitraz poisoning in humans. Vet Hum Toxicol 38(1):28-30.
48. Ulukaya S, et al. 2001. Acute amitraz intoxication in human. Inten Care Med 27(5):930-933.
49. Zwiener RJ, et al. 1988. Organophosphate and carbamate poisoning in infants and children Pediatrics 81(1):121-126. [erratum 1988 May;81(5):683].
50. Lifshitz M, et al. 1997. Carbamate poisoning in early childhood and in adults. J Toxicol Clin Toxicol 35(1):25-27.
51. Sofer S, et al. 1989. Carbamate and organophosphate poisoning in early childhood. Pediatr Emerg Care 5(4):222-225
52. Verhulst L, et al. 2002. Presentation and outcome of severe anticholinesterase insecticide poisoning. Arch Dis Child 86(5):352-355.
53. Weizman Z, et al. 1992. Acute pancreatitis in children with with anticholinesterase insecticide intoxication. Pediatrics 90(2):204-206.
54. Stremski E, et al. 2002. Severe permethrin toxicity in a 19-month child due to inappropriate home treatment for head lice control. J Toxicol Clin Toxicol 40(5):608.
55. Nordt SP, et al. 2000. Acute lindane poisoning in three children. Emerg Med 2000 18(1):51-53.
56. Angle CR, et al. 1968. Neurologic sequelae of poisoning in children. J Pediat 73(4):531-539.
57. Baker MD, et al. 1986. Ingestion of boric acid by infants. Am J Emerg Med 4(4):358-361.
58. Lankosz-L J, et al. 1997. Severe polyneuropathy in a 3-year-old child after dichlorophenoxyacetic herbicide intoxication]. Przegl Lek 54(10):750-752.
59. Fernando R, et al. 1990. An unusual case of fatal accidental paraquat poisoning. Forensic Sci Int 44(1):23-26.
60. Chan TY, et al. 1996. An estimate of the incidence of pesticide poisoning in Hong Kong. Vet Hum Toxicol 38(5):362-364.
61. Gerbaka B, et al. 1998. [Paraquat poisoning in children]. J Med Liban 46(2):93-96.
62. Janssen F, et al. 1976. Paraquat poisoning in a child. Acta Paediatr Belg 29(3):189-192 .
63. Kalabalikis P, et al. 2001. Paraquat poisoning in a family. Vet Hum Toxicol 43(1):31-33.
64. Daisley H, et al. 1999. Homicide by paraquat poisoning. Med Sci Law 39(3):266-269.
65. Lee HL, et al. 1999. Acute poisoning with a herbicide containing imazapyr (Arsenal): a report of six cases. J Toxicol Clin Toxicol 37(1):83-89.
66. Centers Disease Control. 2003. Poisoning by an illegally imported Chinese rodenticide containing tetramethylene- disulfotetramine – New York City, 2002. MMWR 52(10):199-201.
67. Lima JS, et al.1995. Poisoning due to illegal use of carbamates as a rodenticide in Rio de Janeiro. J Toxicol Clin Toxicol 33(6):687-690.
68. Abdollahi M, et al. 1997. A retrospective study of poisoning in Tehran. J Toxicol Clin Toxicol 35(4):387-393.
69. Leveridge YR. 1999. The pattern of poisoning in Costa Rica during 1997. Vet Hum Toxicol 41(2):100-102.
70. Calvert GM, et al. 2003. Acute pesticide-related illnesses among working youths, 1988-1999. Am J Pub Health. 93(4):605-610
71.Azaroff LS. 1999. Biomarkers of exposure to organophosphorous insecticides among farmers' families in rural El Salvador. Env Res 80(2 Pt 1):138-147.
72. Osimitz TG, et al. 1997. Neurological effects associated with use of the insect repellent N,N-diethyl-m- toluamide (DEET). J Toxicol Clin Toxicol 35(5):435-441.
73. Bell JW, et al. 2002. Human exposures to N,N-diethyl-m-toluamide insect repellents reported to the American Association of Poison Control Centers 1993-1997. Int J Toxicol 21(5):341-352.
74. Briassoulis G, et al. 2001. Toxic encephalopathy associated with use of DEET insect repellents: a case analysis of its toxicity in children. Hum Exp Toxicol 20(1):8-14.
75. Centers Disease Control. 1989. Seizures temporally associated with use of DEET insect repellent--New York and Connecticut. MMWR 38(39):678-680.
76. Zadicoff CM. 1979. Toxic encephalopathy associated with use of insect repellent. J Pediat 95:140-142.
77. Lipscomb JW, et al.1992. Seizure following brief exposure to the insect repellent N,N-diethyl-— toluamide. Ann Emerg Med 21(3):315-317.
78. Petrucci N, et al. 2000. Severe neurotoxic reaction associated with oral ingestion of low-dose diethyltoluamide- containing insect repellent in a child. Pediatr Emerg Care 16(5):341-342.
79. Roland EH, et al. 1985. Toxic encephalopathy in a child after brief exposure to insect repellents. Canad Med Assoc J 132(2):155-156.
80. Tenenbein M. 1987. Severe toxic reactions and death following the ingestion of diethyltoluamide- containing insect repellents. JAMA 258(11):1509-1511.
81. Schaefer C, et al. 1992. Intrauterine diethyltoluamide exposure and fetal outcome. Reprod Toxicol 6(2):175-176.
82. Heick HM, et al. 1980. Reye-like syndrome associated with use of insect repellent in a presumed heterozygote for ornithine carbamoyl transferase deficiency. J Pediatr 97(3):471-473
83. Wantke F, et al. 1996. Generalized urticaria induced by a diethyltoluamide-containing insect repellent in a child. Contact Dermatitis 35(3):186-187
84. Wax PM, et al.1994. Fatality associated with inhalation of a pyrethrin shampoo. J Toxicol Clin Toxicol 32(4):457-460.
85. Kramer MD, et al. 1997. An association of herbicide exposure to wheezing among Iowa farm children. Am J Epid 145(11 Suppl):S19.
86. Braun-Fahrlander C. 2000. Allergic diseases in farmers' **children**. Pediatr Allergy Immunol 11 Suppl 13:19-22.
87. Braun-Fahrlander C, et al. 1999. Prevalence of hay fever and allergic sensitization in farmer's children and their peers living in the same rural community. Clin Exp Allergy 29(1):28-34.

88. Pearce M, et al. 2002. The effects of aerial spraying with Bacillus thuringiensis Kurstaki on children with asthma Can J Publ Health. 93(1):21-25.
89. Ackermann-Liebrich UA, et al. 1992. Epidemiologic analysis of an environmental disaster: the Schweizerhalle experience. Env Res 58:1-14.
90. Wasley A, et al. An investigation of unexplained infant deaths in houses contaminated with methyl parathion. Env Health Persp 110(Suppl 6):1053-1056.
91. Kleemann WJ, et al. 1991. Heavy metals, chlorinated pesticides and polychlorinated biphenyls in sudden infant death syndrome (SIDS). Int J Legal Med 104(2):71-75.
92. Althoff H, et al. 1987. [Toxic environmental factors in sudden infant death (SIDS)]. Z Rechtsmed 98(2):103-110.
93. Valery PC, et al. 2002. Farm exposures, parental occupation, and risk of Ewing's sarcoma in Australia: a national case-control study. Can Causes Contr 13(3):263-270.
94. Hum L, et al. 1998. The relationship between parental occupation and bone cancer risk in offspring. Int J Epid 27(5):766-771.
95. Kristensen P, et al. 1996. Cancer in offspring of parents engaged in agricultural activities in Norway. Int J Can 65(1):39-50.
96. Holly EA, et al. 1992. Ewing's bone sarcoma, parental occupational exposures and other factors. Am J Epid 135(2):122-129.
97. Cordier S, et al. 1997. Parental occupation, occupational exposure to solvents and polycyclic aromatic hydrocarbons and risk of childhood brain tumors. Can Causes Contr 8(5):688-697.
98. Cordier S, et al. 1994. Incidence and risk factors for childhood brain tumors in the Ile de France. Int J Can 59:776-782.
99. Schuz J, et al. 2001. Risk factors for pediatric tumors of the central nervous system: results from a German population-based case-control study. Med Ped Oncol 36(2):274-282.
100. Feychting M, et al. 2001. Paternal occupational exposures and childhood cancer. Env Hlth Persp 109(2):193-196.
101. Holly EA, et al. 1998. Farm and animal exposures and pediatric brain tumors. Can Epid Biomark Prev 7(9):797-802.
102. Bunin GR, et al. 1994. Risk factors for astrocytic glioma and primitive neuroectodermal tumor of the brain in young children, Can Epid Biomark Prev 3(3):197-204.
103. Bunin GR, et al. 1990. Occupations of parents of children with retinoblastoma. Can Res 50(22):7129-7133.
104. Fear NT, et al. 1998. Childhood cancer and paternal employment in agriculture: the role of pesticides. Br J Can 77(5):825-829.
105. Shu XO, et al. 1988. A population-based case-control study of childhood leukemia in Shanghai. Cancer 62:635-644.
106. Meinert R, et al. 2000. Leukemia and non-Hodgkin's lymphoma in childhood and exposure to pesticides. Am J Epid 151(7):639-646
107. Kaatsch P, et al. 1996. A case control study on childhood leukemia in Lower Saxony, Germany. Klin Padiatr 208(4):179-185.
108. Magnani C, et al. 1990. Parental occupation and other environmental factors in the etiology of leukemias and non-Hodgkin's lymphomas in childhood: a case-control study. Tumori 76(5):413-419.
109. Kishi R, et al. 1993. [Association of parents' occupational exposure to cancer in children: a case-control study of acute lymphoblastic leukemia]. Sangyo Igaku 35(6):515-529.
110. Reynolds P, et al. 2002. Childhood cancer and agricultural pesticide use: an ecologic study in California. Env Hlth Persp 110(3):319-324.
111. Steinbuch M. 1994. The role of environmental exposures in the etiology of childhood acute myeloid leukemia. Diss Abstr Int [B]; 55(6):2181 Ohio State Univ.
112. Buckley JD, et al. 1989. Occupational exposures of parents of children with acute nonlymphocytic leukemia. Can Res 49:4030-4037.
113. Kerr MA, et al. 2000. Parental occupational exposures and risk of neuroblastoma: a case-control study (United States). Can Causes Contr 11(7):635-643.
114. Olshan AF, et al. 1999. Neuroblastoma and parental occupation. Can Causes Contr 10(6):539-549.
115. Sharpe CR, et al. 1995. Parental exposures to pesticides and risk of Wilms' tumor in Brazil. Am J Epid 141(3):210-217.
116. Leiss JK, et al.1995. Home pesticide use and childhood cancer: a case-control study. Am J Pub Hlth 85(2):249-252.
117. Pogoda JM, et al. 1997. Household pesticides and risk of pediatric brain tumors. Env Hlth Persp 105(11):1214-1220.
118. Davis JR, et al. 1993. Family pesticide use and childhood brain cancer. Arch Env Contam Toxicol 24:87-92.
119. Sinks TH Jr. 1985. N-nitroso compounds, pesticides, and parental exposures in the workplace as risk factors for childhood brain cancer: a case-control study (aromatic amines, ascorbic acid, nitrate). Diss Abstr Int (Sci); 46(6):1888. Ohio State Univ.
120. Alexander FE, et al. 2001. Transplacental chemical exposure and risk of infant leukemia with MLL gene fusion. Can Res 61(6):2542-2546.
121. Ma X, et al. 2002. Critical windows of exposure to household pesticides and risk of childhood leukemia. Env Hlth Persp 110(9):955-960.
122. Lowengart RA, et al. 1987. Childhood leukemia and parents' occupational and home exposures. JNCI 79(1):39-46.
123. Schwartzbaum JA, et al. 1991. An exploratory study of environmental and medical factors potentially related to childhood cancer. Med Ped Oncol 19(2):115-121.
124. Buckley JD, et al. 2000. Pesticide exposures in children with non-Hodgkin lymphoma. Cancer 89(11):2315-2321.
125. Daniels JL, et al. 2001. Residential pesticide exposure and neuroblastoma. Epidemiology 12(1):20-27.
126. Olshan AF, et al. 1993. Risk factors for Wilms tumor. Report from the National Wilms Tumor Study. Cancer 72(3):938-944.
127. McCredie M, et al. 1994. Perinatal and early postnatal risk factors for malignant brain tumours in New South Wales children. Int J Can 56(1):11-15.
128. Heacock H, et al. 2000. Childhood cancer in the offspring of male sawmill workers occupationally exposed to chlorophenate fungicides. Env Hlth Persp 108(6):499-503.
129. Moller H. 1997. Work in agriculture, childhood residence, nitrate exposure, and testicular cancer risk. Can Epid Biomark Prev 6(2):141-144.

Chapter 5
Pesticides and Cancer in Adults

Introduction:
Most pesticide exposure is clinically silent and goes unnoticed. Exposure may result from legal use that does not cause any apparent illness, leading to false assumptions of safety. It is a challenge to study pesticides as a risk factor for cancer in adults since the period of time between exposure and development of disease (clinical latency) is years long. There is also exposure to a large number of pesticides with use patterns changing over a. Other factors to consider are alcohol, tobacco, drugs, and other exposures. In studying agricultural pesticide use on farms, possible contributing factors include exposures to dusts, animals, and fertilizer, among others. Many pesticides are classified as possible or probable human carcinogens (see Appendix G), and little is known the risk of chronic low-level exposures over a working life-time.

Most studies of chronic health effects of pesticides are groups with occupational exposure, such as farmers, farm workers, exterminators, pesticide formulators and factory workers. Fewer studies focus on non-occupational sources of exposure including home, lawn, and garden use, and drift from living near crop growing areas, or near pesticide factories.

Occupational Pesticide Exposure

Agricultural
- Farmers
- Farm workers
- Ground applicators
- Aerial applicators
- Nursery, greenhouse workers

Non-agricultural
- Exterminators (pest control operators, PCOs)
- Formulators
- Factory workers
- Turf , lawn care workers
- Gardeners, landscapers
- Road side sprayers
- Mosquito, vector control

This chapter summarizes studies of pesticides as a risk factor for cancer in adults (cancer in children is discussed in Chapter 7). Study finding summarized in Tables 1-7 are listed by the country where they were done, and with the most recent studies listed first.. See Appendix F for an explanation of how the studies are done and what the numbers and abbreviations mean. There are many factors that can affect study results. See the citations in the reference section for full details.

If the type of cancer is rare or infrequent, or the number of people in the study is small, it may be difficult to find an association between pesticide exposure (increase or decrease), even if it exists. In many of the studies cited in this discussion, increases in risk were found but were not statistically significant. For example, one study found a 30 to 45% increase in risk of non-Hodgkin lymphoma for pesticide illness or pesticide spills on clothing, but it was not statistically significant[136]. Only statistically significant results, and some of borderline significance, are included in this summary.

Because the source and type of exposure can affect the risk of cancer, the summary discusses cancer as follows:

Table 1-A Occupational Agricultural Pesticide Exposure - Increased Risk
Table 1-B Occupational Agricultural Pesticide Exposure - Increased Risk
Table 1-C Occupational Agricultural Pesticide Exposure - Increased Risk
Table 2 Occupational Agricultural Pesticide Exposure - Decreased Risk
Table 3 Non-Agricultural Occupational Pesticide Exposure - Increased and Decreased Risk
Pest Control Operators (PCOs), Exterminators
Table 4 Pesticide Manufacturing and Formulation Exposure - Increased Risk
Table 5 Pesticide Manufacturing and Formulation Exposure - Decreased Risk
Table 6 Environmental, Drift, and Other Non-occupational Pesticide Exposure - Increased Risk
Table 7 Environmental, Drift, and Other Non-occupational Pesticide Exposure - Decreased Risk

Bladder Cancer
Chlordimeform, a cotton insecticide banned by the EPA in 1988, metabolizes to a known bladder carcinogen 4-chloro-o-toluidine. Factory workers manufacturing this pesticide have a strikingly high risk of bladder cancer (SIR 89.7, SIR 53.8, SIR 35.0)[200]. A much lower, but significant, increased risk was found in agricultural researchers (OR

9.3)[41], and workers manufacturing chlorinated hydrocarbons (SMR 7.1)[201]. Farmers[38,41,42], farm workers[39], agricultural extension agents[43], pest control operators[187,188], and people living in wheat crop areas in the midwest[250] are also at increased risk. Several studies found a decreased risk in farmers, both males[42,103], and females[148,163].

Bone Cancer
While no associations have been reported in U.S. farmers or farm workers, increased risk was reported in people living in wheat growing areas of the Midwest[250.] Increased risk was found in female farm workers in Denmark (SIR 6.25)[45], and male farm workers in Japan (SR 1.62) [46].

Brain Cancer
There are reports of increased brain cancer risk in all pesticide exposed groups except factory workers. The highest reported risk in adults is a 670% increase in women living near cranberry bogs in Cape Cod, Massachusetts (OR 6.7)[254]. High risks were found in Chinese female grain farmers (SIR 6.5)53, agricultural researchers in Ireland (OR 4.69)[40], and farm workers in Italy (OR 5.0)[5]. A lower increase was found in agricultural extension agents (PMR 2.08)[43], pest control operators (SMR 2.7)[189], and golf course superintendents (PMR 2.3)[190]. Decreased risk was found in seed disinfection workers[239].

Breast Cancer (female) - Occupational
Increased risk was found in North Carolina farm women who applied pesticides (OR 1.8), which increased by % if they did not use protective equipment (OR 2.0)[61], and in crop farmers[60]. Most other studies of agricultural exposures report a decrease in risk, including U.S. migrant farm workers[129], apple orchard workers[166], Japanese farm workers[46], and Swedish farmers[163]. An increased risk was found in ethylene oxide factory workers (OR 2.55)[206], and a borderline increase in herbicide manufacturers in Germany (SMR 2.15)[204], and in an international cohort of herbicide factory workers (SMR 2.16)[205]. A decreased risk was found in pest control operators in Florida[196].

A recent survey from Canada reporting a 900% increase in risk of breast cancer in farm women was not included in the table. The study participants were not a random sample, but self selected, with breast cancer patients more likely to be included. The numbers were small, and the comparison was to other cancer patients, with no cancer free controls[a].

Breast Cancer (male) - Occupational
Breast cancer is rare in men. The American Cancer Society predicts that in 2003, there will be 1,300 cases, compared to 211,200 in women[b]. Non-significant increase in risk of male breast cancer was found in U.S. farmers in 23 states[58], and in Danish farmers and farm employees[45]. A U.S. case-control study[240], and an international cohort study[209], found no association with herbicide and pesticide exposure.

Breast Cancer (female) - Environmental
The possible relationship between pesticides and breast cancer has been the focus of many studies. Most have been of DDE, the persistent metabolite of DDT that is most prevalent in human tissues. Some studies are done by grouping the women with breast cancer into several categories (usually quartiles (four groups), or quintiles (five groups)), based on the lowest to highest amount of pesticides in the blood or tissue. If the breast cancer rate increases with increasing levels of DDE, and the women with the highest levels of pesticides also have the highest rates of breast cancer, there is an association between the DDE and breast cancer if the findings are statistically significant. Other studies compare the DDE levels between women with and without breast cancer. If the levels are higher in the women with breast cancer there is association with breast cancer if the findings are significant (see Appendix A for an explanation of statistical significance). Studies reporting an increase in risk are shown in Table 9; those reporting a decrease in risk in Table 10.

One investigator concludes that "...exposure to persistent, hormonally active organochlorines during adulthood is not associated with breast cancer risk. The possibility that some organochlorines and especially p,p'-DDE may increase breast cancer aggressiveness deserves further attention"[255]. The American Cancer Society has issued the following

[a] Brophy JT, Keith MM, Gorey KM, et al.2002. Occupational histories of cancer patients in a Canadian cancer treatment center and the generated hypothesis regarding breast cancer and farming. Int J Occ Env Hlth 8(4):346-353.
[b] Cancer Facts and Figures 2003. American Cancer Society.

statement: "While some of these compounds may have other adverse environmental or health effects, organochlorine exposure is not believed to be causally related to breast cancer. Women concerned about possible organochlorine exposure can be reassured that available evidence does not suggest an association between these chemicals and breast cancer."[c]

Colorectal Cancer
High risk of rectal cancer was found in one of the few studies of female pesticide applicators (RR 4.63)[62], and in farmers licensed more than 10 years (OR 4.22)[63]. Pesticide factory workers are at increased risk, including those manufacturing the herbicide alachlor for five years or more (SIR 4.3)[205], and females manufacturing arsenicals (SMR 6.7) [206]. Lower increases were found in farmers[41,55], agricultural extension agents[43], forest consevationists[69], and golf course supertendents[190]. An increase in rectal cancer was found in men living in pesticide use areas[250]. A national study of migrant farm workers[129], and aerial applicators[87] found a decrease in risk.

Eye Cancer
There are reports of high risk in Midwest farmers (OR 6.5, PMR 3.75)[44,64], in women living near agricultural pesticide use areas (SRR 5.77)[278], and in a pesticide manufacturing cohort (OR 2.3)[207]. Non-significant increased risk of uveal melanoma was found for agricultural occupation and self reported pesticide exposureREF.

Hodgkin's Disease
Hodgkin lymphoma is not as strongly associated with pesticides as non-Hodgkin type (see below). The highest reported risk is in creosote factory workers (OR 10.7)[208], and in farmers exposed to herbicides for more than 10 years (RR 8.7)[66]. A doubling or more in risk was found in farmers[42,45,65], and agricultural extension agents[43].

Kidney Cancer
The highest reported risk is in forestry soil conservationists (OR 9.0)[69], and pentachlorophenol factory workers (RR 4.16)[210]. Increases were also found in farmers[63,67,68], and in men living in wheat production areas[250].

Leukemia
Leukemia is frequently associated with pesticide exposure. The highest risk reported is in factory workers manufacturing the herbicide alachlor at a Monsanto facility in Iowa (SIR 28.6)[205]. Among farmers the highest risks were found in New Zealand (OR 10.4)[79], and in Iowa/Minnesota (OR 11.1)[84]. At high risk are female pesticide applicators (SIR 5.6)[62], aerial applicators (RR 3.35)[87], and agricultural extension agents (PMR 5.4)[43]. Lower risks were found in pesticide users in Denmark[71], France[73], Italy[74-78], Sweden[81], and the U.S.[84-86,89]. Farm workers were found to have an increased risk of 59% in California[54], and 90% in Sweden[80]. But most studies of farm workers find a non-significant small increase, no association, or a decrease in risk in risk (see Table 5). There are reports of increased risk in people living near pesticide use areas in Australia[272], Candada[273], the Philippines[274] and the U.S.[275].

Liver and Biliary Cancer
The highest reported risk is in pest control operators (SMR 5.7)[189], and factory workers (SMR 3.9) [201]. At lower increased risk are farmers[45,92-94], malaria sprayers[192], grain millers[91], and women living in wheat production areas[250].

Lung Cancer
Several studies report decreased risk in farmers[dk42, 82,151,163], and farm workers[174,175]. Other studies found an increased risk in farmers[95,97]. Factory workers are at higher risk, with increases reported from DBCP[e 216], arsenicals[206], and a 22% to 46% increase (some borderline, see Table 7) from herbicides, chlordane, and diatomaceous earth[209,211,213-215,217.]. A national cohort study of pest control operators found a 35% increase[194], and a Florida study a borderline significant increase[193].

Malignant Melanoma (Skin)
The highest reported risk is in black farmers in North Carolina (PMR 6.3)[89]. Increased risk was also found in

[c] Calle EE, Frumkin H, Henley SJ, et al. 2002. Organochlorines and breast cancer risk. CA Cancer J Clin 52(5):301-309.
[d] Farmers as a group smoke less than the general population.
[e] Soil fumigant dibromochloropropane (DBCP), a known animal carcinogen, banned continental U.S. in 1979, and Hawaii in 1989.

Australia / Scotland[98], male banana workers in Costa Rica[99], and in Scandinavia[55,100].

Multiple Myeloma

The highest reported risk is an 820% increase in herbicide applicators (SMR 8.2)[195]. Multiple myeloma is more frequently reported in farm workers than other cancers, with a 20% to 80% increase in risk[101-102,105-106,110]. A 340% increase in risk was found if the farm workers were exposed to pesticides (OR 5.2), with a further 270% increase if exposed ten years or more (OR 7.9) [110]. Multiple myeloma is frequently reported in females, who are at greater risk than males[45,53,58,103] (see Table 4b). There are reports of a 23% to 80% increase in farmers[41,100-101,104,111], rising further with pesticide exposure[107-109]. Younger farmers are at greater risk than older farmer[107]. Increased risk was also found in pest control operators[196], golf course superintendents[190], malaria eradication sprayers[192], and agricultural extension agents[43]. No increase in risk has been reported in factory workers or people living near pesticide use areas.

Nasal Cancer

High risk is reported in workers manufacturing chlorophenols for ten years or more (RR 9.07)[221], in female farmers (SPIR 7.4)[112], for daily burning of insecticide coils (OR 7.8)[219], and in workers manufacturing formaldehyde (OR 6.2, OR 4.0)[218-219], chlorophenols (OR 5.9)[220], or herbicides (SMR 4.92)[211]. Farm workers [113-114], farmers [115], and females who live near pesticide use areas (SRR 3.35)[278] were also at increased risk. There are no reports of increases in pest control operators.

Nervous System Cancer

The mortality of pesticide-exposed workers linked to the 1986-1994 National Health Interview Survey found increased risk for nervous system cancers, RR 2.4 (1.3-4.6)

Non-Hodgkin Lymphoma

Non-Hodgkin lymphoma is the cancer most frequently associated with pesticide exposure. The highest reported risk is in factory workers manufacturing the herbicide alachlor at a Monsanto facility in Iowa (SIR 18.6)[225]. High risks are also found in workers manufacturing creosote (OR 9.4)[208], and arsenicals (SMR 8.53)[206]. A 200-500% increase in risk was found in workers manufacturing phenoxy herbicides[208,,222-224], and pentachlorophenol[224.]

A study finding an 800% increase in risk of non-Hodgkin lymphoma in Kansas farmers using 2,4-D (OR 8.0)[152], resulted in this cancer being one of the most studied in agriculture. The focus on phenoxy herbicides was driven by concerns about the potential long term health effects of Agent Orange, a 50-50 combination of 2,4-D and 2,4-5-T used as a defoliant in Vietnam from 1965 to 1972. Studies confirming the association found increased risk in farmers in Illinois[82], Iowa[149-151,153,155], Kansas[152,153,155], Minnesota[151,153,155], Nebraska [153,155,159,160], Washington state[161], Wisconsin[44,162], and in a 24 state cohort[156]. There were also increases in agricultural extension agents[41], soil /forestry conservationists[69], forest herbicide applicators[161], and flour/grain mill workers[90,91]. Other countries reporting an increased risk in farmers are Canada[136-140], France[f141,142], Italy[66,77,143], New Zealand[145], and Sweden[80,146-148] including hairy cell type[c,147]. See Table 4c for specific pesticides related to the increases.

Non-agricultural workers at increased risk are lawn care applicators (SMR 7.1)[192], and golf course superintendents (PMR 2.4)[191]. There are reports of increased risk from living near crop production areas in Australia[272], Canada[252], Finland[276], Italy[277], and the U.S.[235,279].

Ovarian Cancer

There are no reports of ovarian cancer in any occupational group with pesticide exposure. Two studies in Italy in the 1980s found an increase in women living in high atrazine use corn producing areas (RR 2.7)[282], (RR 4.28 bs[g])[283]. A more recent study in Kentucky of women living in areas with high atrazine use on corn found a decrease in risk[301].

Pancreatic Cancer

The highest reported risk is in factory workers manufacturing nitrofen (RR 12.0) and DDT (RR 7.8). In the same factory a 400-500% increase[228,], and 30-60% increase[226-227] was found with other pesticides (see Table 7). High risk was found in gardeners (OR 6.7)[116], in pesticide licensed farmers (OR 5.2)[63], and a lower 10-40% increase in other farmers[44-45,58,92,118]. A doubling or more of risk was found in aerial pesticide applicators[87], and grain/flour mill

[f] Hairy cell leukemia is a rare subtype of non-Hodgkin lymphoma.
[g] Borderline significant.

workers[90-91]. People living in midwest wheat producing areas were at increased risk[250], as were Californians living in the high pesticide use counties of Fresno, Kern, and Tulare. The only pesticide for which the increase was significant was 1,3-dichloropropeneREF. A nonsignificant 60% increase was found in Australian outdoor workersREF. A decrease was found in a national study of U.S. migrant farm workers[129]. No associations were found in pest control operators.

Prostate Cancer

Most risks of prostate cancer from agricultural pesticide exposures are low, from a 12-70% increase in farmers[120-124], a 22-45% in farm workers[46,53], and 50% in agricultural extension agents[43]. One study found a doubling of the risk (RR 2.23)[119]. A recent report from the Agricultural Health Study found a 14% increased risk in Iowa and North Carolina farmer applicators. The pesticide significantly associated with increased risk in all farmers was methyl bromide in those with high level exposure. In those with a family history of prostate cancer, butylate, chlorpyrifos, coumaphos, fonofos, and phorate in those with a family history of prostate cancer. A study in North Dakota found mean survival in prostate cancer patients was for those without. Another recent study in Italy found increased risk in farmers exposed to, whose effects could not be well separated. Increased risk was found in black workers manufacturing DDT[229]. No associations were found in pest control operatorsREF, or in people living near a pesticide use areaREF.

Soft Tissue Sarcoma

The highest risks reported are in a cohort of factory workers manufacturing herbicides (OR 10.3)[231], in a cohort of herbicide sprayers (SMR 8.2)[197], and in U.S. chlorophenol workers (OR 7.78)[237]. A 300-680% increase was found in other herbicide manufacturing workers[197,230,233-236], in gardeners[125] and in orchard / greenhouse workers[53]. Other studies of farmers[42,146], and farm workers[46], found a lower increased risk, and others a decrease in risk or no association (see Table 7). A high risk of this rare cancer was found in people living in an area of chlorophenol contamination in Finland (RR 8.9)[279], and in men living near a pesticide factory in Spain (SIR 5.5)[252]. Men living in rice crop areas had a lower increase in risk[280].

Stomach Cancer

Most risks of stomach cancer in agriculture are low, ranging from a 25-69% increase in farm workers[45-46,54-55,128-129], to a 24-88% increase in farrmers[44-45,58,92,149]. Higher risks were found in forestry workers (OR 4.3)[127], and pesticide licensed farmers (OR 2.62)[g63]. Although aerial pesticide applicators were found to have a 32% decrease in risk, all three gastric cancer deaths were in pilots with the most flight hours (more than 1,280)[180]. Factory workers manufacturing pentachlorophenol[210] and phenoxy herbicides[128] were at increased risk. Hungarian men living in a high pesticide use village were at increased risk (RR 3.2)[287], as were people living in Midwest wheat producing areas[250]. No associations were found in pest control operators, or people living in California's Central Valley where drinking water wells were contaminated with DBCP [(g)313]

Testicular Cancer

There are few studies of pesticides as a risk factor for testicular cancer. Unlike earlier studies in Texas reporting a high risk in farmers (OR 6.27) and farm workers (OR 5.1)[135], most find less than a doubling of the risk[53,130-134], or a decreased risk[130-134,184-185]. An increase in risk was found in pest control operators (SIR 2.5)[196], and factory workers manufacturing methyl bromide[217]. No associations have been reported for people living in high pesticide use areas.

Thyroid Cancer

Thyroid cancer is infrequently reported in association with occupational pesticide exposure. There are reports of an increase in Midwest farmers (SMR 2.9)[42], and a 60% increase in female farmers in Denmark (RR 1.6)[45]. No association have been reported in pest control operators or factory workers. An unusual finding is an increased risk in males, but not females, exposed to hexachlorobenzene from living near a solvent factory in Spain (SIR 6.7)[252], in an area of pesticide use [278], and in wheat producing areas[250].

Table 1-A
Occupational Agricultural Pesticide Exposure - Increased Risk
(See Appendix F for explanation of the table)

Bladder Cancer	
France vineyard farmers[1]	RR 1.17
France agricultural workers[2]	OR 4.6
Ireland agricultural research workers[3]	OR 9.31
US agricultural extension agents[4]	PMR 2.72
US Iowa, North Carolina farmers[5]	SMR 2.9
US Iowa farmers[6]	SMR 1.37
US Wisconsin farmers[7]	PCMR 1.55
Bone Cancer	
Denmark female farmers/farm employees[8]	SIR 6.25
Japan male agric. wrkrs (incl.soft tiss. sarcoma)[9]	SPR 1.62
Brain Cancer	
Canada farmers fuel use - trend significant[10]	OR 2.11 bs*
France farmers exposed to pesticides[11]	RR 1.10
Ireland agricultural research workers[3]	OR 4.69
Italy farmers pesticide licensed[12]	SIR 2.1
Italy agricultural workers (after 1960)[13]	OR 5.0
New Zealand male livestock farmers[14]	OR 2.59
All farmers	OR 1.38
Norway grain farmers[15]	RR 1.51 bs*
Shanghai female grain farmers[16]	SIR 6.5
Pesticide exposed	SIR 3.6
Sweden (glioma) farm supervisor - male[17]	RR 2.34 bs
Forestry supervisor - male	RR 1.63
Horticultural worker - male	RR 1.75
Agricultural worker - female	RR1.22 bs
US agricultural extension agents[4]	PMR 2.08
US California UFW union members[18]	MbOR 1.57 bs*
US California farm workers non-white[19]	PCMR 1.55
US Meta-analysis 33 studies[20]	RR 1.30
US Missouri agric production male[21]	OR 1.5 bs*
US 4 states farm women pesticide exposed[22]	OR 1.2
US 23 states white male farmers[23]	PCMR 1.15
US 24 states women crop farmers[24]	PMR 1.9
Breast Cancer *(female)*	
Canada British Columbia crop farmers[25]	Increase
Canada Ontario women >55 who ever farmed[26]	OR 9.05
Serbia women pesticide exposed[27]	RR 4.25
US N. Carolina farm women applied pesticides[28]	OR 1.8
Colorectal Cancer	
Iceland all pesticide applicators [29]	SIR 2.94
Licensed users only	RR 4.63
Italy farmers pesticides licensed >10 years[30]	OR 4.22
US agricultural extension agents[4]	PMR 1.46
US California farm owners/managers[19]	PCMR 2.2
US Iowa farmers[6]	SMR 1.22
US soil conservationists[31]	PMR 1.5
15 years or more in forestry	OR 1.9
Eye Cancer	
US Illinois farmers[32]	OR 6.5
US Wisconsin farmers[7]	PMR 3.75
US agricultural expos. (uveal melanoma)[33]	OR 2.18 ns
Hodgkin Disease	
Italy male farmers/farm employees[8]	OR 2.91
Italy farmers pesticide exposed[34]	OR 3.2
Italy agricultural herbicide exposure >10 yrs[35]	RR 8.7
Norway orchard/greenhouse workers[15]	RR 1.85 bs*
US agricultural extension agents[4]	PMR 2.72
US Iowa, North Carolina farmers[5]	SMR 2.9
US Iowa farmers[6]	SMR 1.37
US Wisconsin farmers[7]	PCMR 1.55
Kidney Cancer	
Canada men pesticide, herbicide exposure[36]	OR 1.6, 1.8
Denmark men ≥ 20 yrs expos. insect/herbicides[37]	OR 3.9 bs
Italy copper sulfate exposure[38]	OR 2.7
Italy farmers pesticide licensed[30]	OR 2.0
Italy farmer/farm employee females[8]	OR 4.23
Male farmers/farm employees	OR 1.46
US Iowa farmers[6]	OR 1.22
US soil conservationists ≥ 15 years in forestry [31]	OR 9.0
US 23 states white male farmers[23]	OR 1.10
Leukemia	
Canada British Columbia farmers[39]	PCMR 1.22
Denmark male gardeners pesticide exposed[40]	SMbR 2.75
Denmark female farmers/farm employees[8]	SIR 2.22
France farmers pesticide exposed[41]	SMR 1.33
France herbicide exposure more than 10yrs[42]	OR 6.0
Insecticide exposure more than 10 yrs	OR 4.0
Italy male farmers pesticide licensed[43]	SMR 2.43 bs*
Wives of licensed farmers	SMR 3.14
Italy farmers pesticide exposed[44]	OR 4.9
Italy farmers/breeders insecticide exposure[45]	OR 2.46
Carbamate exposure	OR 3.08
Organophosphate exposure	OR 2.9
Italy animal breeding workers[46]	OR 1.79
Italy women pesticide exposed[47]	OR 4.4
New Zealand livestock farmers[48]	OR 3.0
Acute monocytic 65 yrs and older	OR 10.4
Norway male dairy farmers[15]	RR 1.76
Sweden farmers (ANLL)[49]	SIR 5.0
Gardeners (CML)	SIR 4.0
Agricultural workers (CML)	SIR 1.9
Sweden farmers DDT exposed (CLL)[50]	RR 6.1
US aerial pesticide applicators[51]	RR 3.35
US agric. extension agents (lymphocytic)[4]	PMR 5.4
US farmers 23 states white males[(b)23]	PCMR 1.27
US farmers 26 states white males (lymphocytic)[24]	PMR 1.14
US flour mill worker 10 to 20 years[52]	SMR 1.94
US California UFW[(a)] union members[18]	OR 1.59
US Illinois farmers[32]	OR 1.51
US Iowa farmers (CLL)[53]	OR 1.70
US Iowa, Minnesota farmers OP use[54]	OR 2.2
Ever handle crotoxyphos	OR 11.1
Ever handle dichlorvos	OR 2.0
Ever handle pyrethrins	OR 3.7
Used DDT on animals	OR 2.1
US Iowa, Minnesota farmers dichlorvos use[55]	OR 1.8
US Iowa, Minnesota farmers herbicide use[56]	OR 1.86
Insecticide exposure	OR 1.50
US Nebraska farmers born after 1900[57]	OR 1.24
High insecticide use counties	OR 1.95
US North Carolina black farmers[58]	PMR 1.2
US Wisconsin farmers[7]	PMR 1.10
Liver and Biliary Cancer	
Canada British Columbia farmers[59]	PCMR 1.73
Denmark female farmers/farm employees[8]	SIR 2.66
Sweden grain millers[60]	SIR 2.38
US New Jersey agricultural production[61]	RR 2.08
US 5 states pesticide exposed farmers[62]	RR 2.4 bs*

* bs = borderline significance
(a) United Farm Workers (b) PCMR 1.45 in females borderline sig.

continued in Tables 1-B, and 1-C

Table 1-B
Occupational Agricultural Pesticide Exposure - Increased Risk
(See Appendix F for explanation of the table)

Lung Cancer	
Canada farmers herbicide exposure[63]	Increase
China farmers[64]	OR 1.6 bs*
China men exposed to pesticides[65]	OR 3.29
US Missouri farmers pesticide exposure[66]	OR 2.3
Malignant Melanoma (Skin)	
Australia, Scotland pesticide exposure[67]	RR 3.6
Costa Rica male banana workers[68]	SIR 1.97 bs
Norway agricultural pesticide exposure[15]	RR 1.37
Sweden farmers[69]	SMR 1.39
US N. Carolina black farmers[58]	PMR 6.3
Multiple Myeloma	
Canada farmers, prairie provinces[70]	RR 1.69
Denmark farmers/farm employees male, female[8]	SIR 3.3,1.57
England agricultural workers[71]	RR 1.8
France farmers[1]	SMR 1.59
Italy female farmers[72]	RR 2.4
Italy female farm workers, tree fruit[73]	OR 1.75
Any chlorinated pest.expos,, DDT exposure	OR 1.6,2.6 bs
New Zealand farmers diagnosed < age 65[14]	OR 2.2
Norway farmers/agricultural workers[15]	RR 2.61
Sweden forestry workers[49]	SIR 3.6
Sweden farmers[74]	SIR 1.4
Sweden farm workers[75]	SIR 1.4
Sweden agricultural workers[76]	SMR 1.2
US agricultural extension agents[4]	PMR 1.9
US national farming herb/pest. expos. (trend ns)[77]	OR 4.3
US Iowa farmers[6]	OR 1.5
US Wisconsin farmers[7]	PMR 1.23
US Wisconsin farmers insecticide areas[78]	OR 1.9
US 4 states farmers pesticide exposed[79]	RR 2.6
US 4 states farm workers pest. expos.≥10 yrs[80]	OR 7.9
Employed in forestry	OR 2.5
US farmers 23 states white males, white females[23]	PCMR 1.15,1.78 bs
US farners 26 states white male s, livestock[24]	PMR 1.29
US farmers meta-analysis 32 studies[81]	RR 1.38
Nasal Cancer	
Denmark female farmers[82]	SPIR 7.4
Europe male, female orchard workers [83]	OR 3.72, 1.69
France farm workers males, females[84]	OR 2.2, 4.9 bs*
Sweden farmers died 1974-79[85]	RR 2.1
Nervous System Cancer	
US National Mortality 1986-1994[86]	RR 2.4
US 4 states females insecticide/fungicide expos.[87]	OR 1.2
(Non-Hodgkin Lymphoma See Table 1-C)	
Pancreatic Cancer	
Canada British Columbia farmers[39]	PCMR 1.2 bs*
Finland male gardeners[88]	OR 6.7
Italy farmers pesticide licensed vs non-licensed[30]	OR 5.18
Licensed vs entire cohort of farmers	OR 3.78
Italy male farmers/farm employees[8]	OR 1.42
Spain pesticide exposure[89]	OR 3.17
US aerial pesticide applicators[51]	RR 2.71
US flour mill workers ≥ 25 years[52]	OR 2.2
US grain millers[90]	PMR 1.91
US Iowa farmers[53]	SMR 1.23
US Louisiana farmers pesticide exposed[91]	OR 1.39
US Wisconsin farmers[7]	PMR 1.20
US 3 states (GA,MI,NJ) pest. expos. trend sig[92]	OR 1.4
Fungicide exposure blacks, whites	OR 1.5, 1.4 bs
US farmers 23 states males white, black[23]	PCMR 1.13,1.2 bs
Prostate Cancer	
Canada farmers pesticide exposed[93]	RR 2.23
Canada Alberta farmers[94]	OR 1.31
Canada British Columbia farmers[70]	PCMR 1.13
England / Wales farmers[95]	PMR 1.12
Italy applied agric. pesticides[96]	OR 1.7
Italy farmers organochlorine insecticides[97]	OR 2.5
DDT exposure, Dicofol exposure	OR 2.1, 2.8
Japan agricultural work[9]	SPR 1.22
Netherlands agric. pest. expos.[98]	Increase
Norway orchard/greenhouse workers[52]	RR 1.45
Sweden agric. pesticide applicators[99]	SIR 1.12
US agricultural extension agents[4]	PMR 1.5
US Calif. white farmers/managers[19]	PCMR 1.22
US Missouri farmers[100]	OR 1.33
US Illinois farmers[101]	OR 1.15 bs
US Iowa, North Carolina farmers[102]	SIR 1.14
Methyl bromide high exposure group	OR 3.4 7
Butylate, Chlorpyrifos exposure	OR 1.93, 1.65
Coumaphos, Fonofos exposure	OR 2.58, 2.04
Phorate exposure	OR 1.64
US N Dak farmers pest expos. median surv.[103]	11.3 months
No pesticide expos. median survival	20.1 months
US forestry soil conservationists[31]	PMR 1.6
US farmers 26 NOMS[(a)] states ,blacks[104]	OR 1.4
US farmers 23 states whites[23]	PCMR 1.18
Soft Tissue Sarcoma	
Denmark male gardeners[40]	SMbR 5.29
Japan male agric. workers (includes bone)[9]	SPR 1.62
Norway female orchard/grnhse workers[15]	RR 3.9
Sweden farmers, gardeners[105]	OR 5.1, 4.1
US Iowa, N Carolina farmers, spouses[5]	SMR 1.6, 1.1
US Kansas farmer pesticide applicators[106]	OR 1.9
Stomach Cancer	
Canada British Columbia farmers[59]	PCMR 1.36
Italy forestry workers[107]	OR 4.3 bs*
Italy farmers pesticide licensed >10 yrs[30]	OR 2.62
Italy farmers/farm employees males [8]	OR 1.25
Japan farm workers female s[9]	SPR 1.37
US California UFW[(a)] union members[18]	MbOR 1.69
US Calif. white farmers, farm workers[19]	PCMR 2.02, 1.34
US Iowa farmers[6]	OR 1.3
US Michigan agriculture white males[108]	OR 2.6
US Wisconsin farmers[7]	PMR 1.24
US farmers 23 states non-white females[23]	PCMR 1.88
US farmers 24 states migrant workers[109]	PCMR 1.22
White workers only	PCMR 1.38
Testicular Cancer	
England, Wales farm owners/managers[110]	OR 1.85
England, Wales farm owners, managers[111]	OR 1.89 bs*
Norway orchard /greenhouse workers[15]	RR 1.63
Sweden farmers (embryonal)[112]	OR 3.1
Farmer use of deet repellent	OR 1.7
Sweden agricultural pesticide applicators[113]	SIR 1.55 bs*
US black farmers who grew up in the South[114]	OR 1.4
US Texas farming, agricultural work[115]	OR 6.27
Thyroid Cancer	
Denmark female farmers/farm employees[8]	SIR 1.6
US Iowa, North Carolina. farmers[5]	SMR 2.9

* bs = borderline signif. (a) National Occupational Mortality Surveillance

Conntinued Table 1-C

Table 1-C
Occupational Agricultural Pesticide Exposure - Increased Risk
(See Appendix F for explanation of the table)

Non-Hodgkin Lymphoma	
Canada farmers raising bison/elk/ostriches[116]	OR 3.26
4 to 15 years living on a farm	OR 2.15
More than 13 head of swine	OR 1.96
Diesel fuel/exhaust exposure	OR 1.52
Canada farmers herbicide use[117]	OR 1.38
2,4-D , Dicamba use	OR 1.32, 1.88
Mecoprop, malathion use	OR 2.33, 1.83
Organophosphate, carbamate use	OR 1.73, 1.92
Aldrin, carbaryl, DDT, lindane use	OR 2.11
Amide fungicides, CCl4 fumigant use	OR 2.42
Canada farmers 8 provinces herbicide use[118]	OR 1.3 bs*
Canada farmers heavy herbicide use[119]	RR 2.1
Canada farmers herbicide use ≥100acres[120]	RR 2.14
France pest. users (hairy cell leukemia[a])[121]	OR 1.5
Organophosphate exposure (non-smokers)	OR 7.5
France farmers(hairy cell leuk[a]) males, females[122]	OR 2.0, 2.7
Italy animal breeders[46]	OR 1.79
Italy farmers triazine herb. exposure > 18 yrs[123]	OR 9.3 bs*
Italy male farmers/farm employees[8]	OR 1.59
Italy agriculture herbicide exposure 1-10 yrs[35]	RR 2.6
Herbicide exposure 10 years or more	RR 5.2
New Zealand orchard farmers[124]	OR 3.7
New Zealand farmers < age 65[125]	OR 1.76
Sweden fungicide use[126]	OR 3.11
Glyphosate herbicide use	OR 3.04
MCPA herbicide use	OR 2.62
Wood preservative use	OR 1.88
Any herbicide use	OR 1.75
Any insecticide use	OR 1.43
Sweden farmers (hairy cell leuk.[a]) fungicide use[127]	OR 3.8
Herbicide use	OR 2.9
Insecticide use	OR 2.0
Sweden female animal breeders[80]	SIR 5.3
Sweden dairy workers[128]	SIR 1.8
US agricultural extension agents[41]	PMR 2.3
US farmers methyl bromide use[129]	OR 2.82
Chloramben use	OR 2.2
Herbicide use	OR 2.06
Insecticide use	OR 1.90
Pentachlorophenol use	OR 1.86
DDT use	RR 1.5
US farmers 4 midwest states handled DDT[130]	OR 1.6
Handled DDT ≥5 days/year (Nebraska)	OR 2.6
US farmers 23 states white males[23]	PCMR 1.2
US farm managers 24 states[131]	SMR 6.3
US farmers 4 states organophosphate use[132]	OR 2.8
US farmers 26 NOMS[(a)] states white ♂ livestock	PMR 1.17
US farmers meta-analysis 6 studies[133]	RR 1.34
US farmers meta-analysis 36 studies[134]	RR 1.10
Central US farmers only	RR 1.26
US flour mill workers after 25 years[52]	SMR 9.4
US grain millers[91]	PMR 2.02
US soil conservationists ≥15 yrs in forestry[31]	OR 11.2
US Illinois farmers Winnegabo county[135]	SMR 2.65
US Iowa farmers[136]	OR 1.3
US Iowa farm women[137]	RR 1.89
US Iowa, Minnesota farmers DDT use[138]	OR 1.5
Chloramben use	OR 2.2
US Iowa, Minnesota exposure methyl bromide[56]	OR 2.82
Herbicide exposure	OR 2.06
Insecticide exposure	OR 1.90
US Kansas farmers mix/apply herbicides[139]	OR 8.0
Herbicide exposure > 20 days per year	OR 6.0
US Missouri farmers[100]	OR 1.4
US Nebraska female farrmers pest. exposed[140]	OR 4.5
Pesticide use dairy cattle	OR 3.0
Organochlorine use	OR 1.6
US Nebraska farmers organophosphate us[141]	OR 1.9
Carbamate use	OR 1.8
US Nebraska 2,4-D use >20 days/year[142]	OR 3.0
US Utah farmers diagnosed 1952-65	OR 6.6
Diagnosed 1966-1971	OR 3.1
US Washington state farmers[143]	OR 1.33
Forest herbicide applicators	OR 4.8
DDT exposure	OR 1.8
US Wisconsin farmers insecticide use[144]	OR 6.6
Wheat farmers, general agriculture	OR 4.4, 3.2
Farmers younger than 65 at diagnosis	OR 1.67

* bs = borderline significance
(a) Hairy cell leukemia is a rare subtype of non-Hodgkin lymphoma.
(b) National Occupational Mortality Surveillance

Table 2
Occupational Agricultural Exposure – Decreased Risk or No Association Found
(See Appendix F for explanation of the table)

Bladder Cancer	
Italy farmers[68]	RR 0.6
US Iowa, North Carolina farmers[5]	SMR 0.57
US Iowa farm women[119]	RR 0.33
Bone Cancer	
US Wisconsin farmers[44]	No association
Brain Cancer	
Europe farm workers[145]	OR 0.66
Europe farm animal contact[163]	No association
Italy farmer pesticide licensed[63]	No association
US farmers ,CNS[(a)] lymphoma[146]	No association
Breast Cancer	
Denmark gardeners[71]	No association
Japan farm workers[46]	SPR 0.73
Sweden female farmers[163]	SIR 0.83
US 24 states migrant workers[128]	Decrease
US female applicators using PPE[(b)] [147]	OR 0.8
US Washington apple orchard worker[148]	OR 0.75
Colorectal Cancer	
Italy farmers[65]	RR 0.6
Sweden male farmers[149]	SIR 0.8
Females	OR 0.9
Sweden female farmers[163]	OR 0.86
US aerial applicators[82]	RR 0.51
US 24 states migrant workers[129]	Decrease
Hodgkin Disease	
Canada farmers pest. expos >10 hrs/yr[150]	OR 0.85
Potential pesticide exposure	OR 0.96
Italy farmers pesticide licensed[151]	No association
US Kansas farmers[112]	No association
Kidney Cancer	
Finland farmers[152]	Decrease
Sweden female farmers[163]	SIR 0.81
Sweden pesticide applicators[153]	SIR 0.53
US California farmers [55]	No association
US Wisconsin farmers[44]	No association
US 24 states migrant workers[128]	No association
Leukemia	
Canada poultry farmers[154]	No association
US 16 states back farmers[155]	OR 0.7
Liver and Biliary	
Japan farm workers[46]	SPR 0.64
Lung Cancer	
Brazil farm workers[156]	No association
Sweden female farmers[163]	SIR 0.46
US Iowa farm women[151]	RR 0.32
US Iowa, North Carolina farmers[42]	SMR 0.3
US Illinois farmers[86]	SMR 0.82
US Washington apple orchard workers[157]	No association
Non-Hodgkin Lymphoma	
Canada agricultural pesticide exposure[158]	No association
Italy farmers pesticide licensed[74]	SMR 0.90
Italy farmers[159]	No association
Sweden female farmers[163]	SIR 0.78
US female farmers[161]	RR 0.93
US Iowa, North Carolina farmers spouses[42]	No association
US North Carolina farmers/farm workers[160]	No association
High pesticide use counties	No association
Multiple Myeloma	
Canada British Columbia farmers[92]	No association
US aerial pesticide applicators[82]	RR 0.23
Nasal Cancer	
Sweden farmers[176]	RR 0.42
Pancreatic Cancer	
US 24 states non-white migrant workers[128]	Decrease
Prostate Cancer	
US Iowa farmers[161]	No association
US California farm workers[55]	No association
Stomach Cancer	
US aerial pesticide applicators[162]	SMR 0.68[(d)]
Soft Tissue Sarcoma	
England/Wales farming/forestry workers[163]	No association
Italy farm employment[164]	OR 0.8
Pesticide exposure	OR 0.4
Italy male rice weeders, herbicides[165]	OR 0.91
Sweden female farmers[163]	SIR 0.62
Sweden farming, forestry workers[106]	OR 0.9
US Kansas farmers[112]	No association
Testicular Cancer	
Canada farmers[166]	OR 0.89
England/Wales farm workers[130]	OR 0.9
US Washington farmers, gardeners[167]	RR 0.6
US currently a farmer[134]	OR 0.6
Ever a farmer	OR 0.9
Thyroid Cancer	
Sweden horticultural workers[168]	Decrease

a Central nervous system
b Personal protective equipment (mask, gloves etc.)
c All three gastric cancer deaths occurred in those with the most flight hours (more than 1,280)

Table 3
Non-Agricultural Occupational Pesticide Exposure - Increased and Decreased Risk
Pesticide Applicators, Pest Control Operators (PCOs), Exterminators
(See Appendix F for explanation of the table)

Increased Risk		Decreased Risk	
Bladder Cancer		**Breast Cancer** (*female*)	
England/Wales PCOs[a] 6[169]	OR 2.4 bs	US Florida licensed PCOs[a] [179]	Decrease
US 40 states applicators[170]	SMR 2.77	Colómbia DDT exposure[258]	Decrease
Brain Cancer		**Kidney Cancer**	
Italy PCOs[171]	SMR 2.7	Sweden applicators[172]	SIR 0.53
US golf course superintendents[172]	PMR 2.3	**Non-Hodgkin Lymphoma**	
Colorectal Cancer		Finland herbicide applicator cohort[181]	SMR 0.42
Iceland pesticide applicators entire cohort[29]	SIR 2.94	US Florida licensed PCOs[a][178]	No association
Licensed users only	RR 4.63	**Liver and Biliary Cancer**	
US golf course superintdents[172]	OR 1.75	Sweden applicators[172]	OR 0.45
Leukemia		**Lung Cancer**	
Iceland female applicators only[29]	SIR 5.6	Italy PCOs[a][171]	SMR 0.5
Australia outdoor workers (myeloid) high expos. grp[173]	SMR 20.9	Sweden applicators[172]	OR 0.50
Liver and Biliary Cancer		**Pancreatic Cancer**	
Italy PCOs[a][171]	SMR 5.7	Sweden applicators[172]	SIR 0.5
Sardinia malaria sprayers[174]	PMR 2.4	**Soft Tissue Sarcoma**	
Lung Cancer		Sweden applicators[182]	RR 0.9
US Florida exterminators less than age 40[175]	OR 2.4 bs*	US Florida licensed PCOs[a] [197]	No cases
US national cohort PCOs[a] [176]	SMR 1.35		
Lymphoma			
US lawn applicators more than 3 years[177]	SMR 7.1		
US golf course superintdents[172]	PMR 2.4		
Multiple Myeloma			
Netherlands herbicides[178]	SMR 8.2		
Sardinia malaria sprayers[174]	PMR 3.4		
US Florida licensed PCOs[a][179]	SIR 2.5		
US golf course superintendents[172]	PMR 2.9		
Pancreatic Cancer			
Australia outdoor workers DDT exposed[173]	SMR 5.3		
Soft Tissue Sarcoma			
International cohort herbicide sprayers[180]	SMR 8.2		
Testicular Cancer			
US Florida licensed PCOs[a][179]	SIR 2.5		

a Pest control operators, exterminators

Table 4
Pesticide Manufacturing and Formulation - Increased Risk
(See Appendix F for explanation of the table)

Bladder Cancer	
Denmark chlordimeform[183]	SIR 35.0
Germany (East) chlordimeform[169]	SIR 89.7
Germany (West) chlordimeform[169]	SIR 53.8
US organochlorines[184]	SMR 7.1
US agricultural chemicals[185]	OR 3.3
Breast Cancer (*female)*	
Germany herbicides[186]	SMR 2.15 bs*
International cohort herbicide workers[187]	SMR 2.16 bs*
US New York ethylene oxide[188]	SMR 2.55
Colorectal Cancer	
US Iowa alachlor factory[189]	SIR 4.3
5 years since first exposure	SIR 5.2
US Maryland female arsenates workers[190]	SMR 6.7
Eye Cancer	
US pesticide factory workers[191]	OR 2.3
Formaldehyde workers	OR 2.9
Hodgkin Disease	
Sweden creosote workers[192]	OR 10.7
Kidney Cancer	
International herbicide cohort[193]	SMR 1.6
US Michigan pentachlorophenol workers[194]	RR 4.16
Leukemia	
England phenoxy herbicides[195]	SMR 1.7 bs*
US Iowa alachlor workers[207]	SIR 25.0
Most heavily exposed	SIR 28.6
Sweden ethylene oxide[196]	SIR 2.44
Liver and Biliary Cancer	
US organochlorines[202]	SMR 3.9
England phenoxy herbicide cohort[213]	SMR 1.15
Lung Cancer	
England 4 pesticide factories[197]	SMR 1.34
England phenoxy herbicide cohort[213]	SMR 1.15 bs*
International herbicide cohort[211]	SMR 1.12 bs*
US diatomaceous earth workers[198]	SMR 1.4
US Michigan DBCP workers[199]	OR 3.3
US Illinois chlordane/others[200]	SMR 1.22
Increasing years of exposure	SMR 1.46
US Maryland male arsenate workers[208]	SMR 2.65
US Michigan/Arkansas pesticide factories[201]	SMR 1.31 bs*
Nasal, Sinonasal Cancer	
England herbicide cohort[213]	SMR 4.93
Europe female formaldehyde workers[202]	OR 6.2
Males	OR 3.0
Phillippines formaldehyde[203]	OR 4.0
US chlorophenol workers[204]	OR 5.9
US. chlorophenol workers[205]	OR 1.94
Exposed 10 years or more	OR 9.07
Non-Hodgkin Lymphoma	
Germany cohort phenoxy herbicide workers[206]	SMR 3.26
20 years or more since first exposure	SMR 4.25
Sweden herbicide workers[247]	OR 3.7
MCPA	OR 2.7 bs*
Phenoxy herbicides	OR 1.5 bs*
Sweden phenoxy herbicides[207]	OR 5.5
Pentachlorophenol	OR 4.8
Phenoxy herbicides	OR 4.9
Creosote	OR 9.4
US Iowa alachlor factory workers[208]	SIR 18.6
US Maryland male arsenate workers[208]	SMR 8.53
US ethylene oxide males[209]	Increase
Pancreatic Cancer	
Spain all pesticide workers[117]	OR 3.17 bs*
Arsenical exposure only	OR 3.4 bs*
US 24 states formaldehyde cohort[210]	OR 1.2-1.4
US Philadelphia nitrofen[211]	RR 12.0
DDT	RR 4.8-7.8
Ethylan	RR 5.0
Nitrophenol	RR 4.5
DDD	RR 4.3
Carbon tetrachloride	RR 4.1
Dinocap	RR 4.1
Prostate Cancer	
US black DDT workers[212]	Increase
Soft Tissue Sarcoma	
US chlorophenol workers[213]	OR 1.79
Exposed for 10 years or more	OR 7.78
Sweden phenoxy herbicides[214]	OR 3.0
International herbicide[215]	OR 10.32
Denmark herbicide work more than 10 years[216]	SIR 6.4
US Alabama herbicide factory[217]	SMR 4.84
Europe herbicide worker 10-19 yrs[198]	SMR 6.06
Sweden chlorophenols[218]	RR 5.25
Pentachlorophenol	RR 3.85
2,4,5-T	RR 2.94
Phenoxy herbicides	RR1.80
Sweden phenoxy herbicide[219]	RR 6.8
New Zealand herbicide workers[220]	RR 1.3
Stomach Cancer	
Sweden all herbicides[221]	OR 1.56
Phenoxy herbicides	OR 1.70
US Michigan pentachlorophenol[2129]	RR 3.63
Testicular Cancer	
US Michigan /Arkansas pesticide factories[219]	SMR 17.99[(a)]

* bs = borderline significance

a Two deaths in workers with methyl bromide as the only exposure in common.

Table 5
Pesticide Manufacturing and Formulation - Decreased Risk or No Association
(See Appendix A for information on using this table)

Brain Cancer	
Sweden seed disinfection workers[222]	Decrease
Breast Cancer (*male*)	
US male pesticide workers[223]	Decrease
Leukemia	
England/Wales ethylene oxide[(a)] workers[224]	Decrease
Germany ethylene oxide workers[225]	Decrease
US ethylene oxide workers[227]	Decrease
Liver/Biliary Cancer	
Netherlands dieldrin exposure[226]	No association
Lung	
US Illinois chlordane workers[227]	Decrease[b]
Non-Hodgkin Lymphoma	
Sweden insecticides[228]	No association
International cohort herbicide workers[198]	No association
US female ethylene oxide[(a)] workers[227]	Decrease
Pancreatic Cancer	
US ethylene oxide[(a)] workers[229,230]	Decrease
US ethylene oxide [(a)] workers[227]	Decrease
Soft Tissue Sarcoma	
Sweden chlorophenol exposure[233]	No association
Netherlands cohort herbicide workers[231]	No cases
Stomach Cancer	
England/Wales ethylene oxide[(a)] [243]	Decrease
US ethylene oxide[(a)] [227]	Decrease
US herbicide and other pesticide workers[127]	No association
US male ethylene oxide[(a] workers[207,208]	Decrease

a A gas used to sterilize hospital equipment.
b A later study found a significant increase[218]

Table 6
Environmental, Drift, and Other Non-occupational Pesticide Exposure - Increased Risk
(See Appendix F for explanation of the table)

Bladder Cancer	
US chlorinated water users[232]	OR 1.43
Bone Cancer	
US 4 states[(a)] wheat areas[233]	Increase
Brain Cancer	
Canada living in pesticide use area[234]	Increase
Spain males living near HCB[(b)] factory[235]	SIR 2.7 bs*
Sweden living near farm pesticide area[236]	OR 2.4 bs*
US Cape Cod females near cranberry bog[237]	OR 6.7
US states[(a)] males living wheat crop areas[251]	Increase
Breast Cancer (*female*)	
Canada DDE levels (invasive, large size)[238]	OR 3.5
Canada DDE fat levels ER⁻[239]	OR 2.4 bs*
Colómbia Bogotá DDE levels[240]	OR 1.9
Denmark dieldrin decreased survival [241,242]	OR 2.6
Denmark dieldrin levels[243]	OR 2.2
Finland β-HCH[©] fat levels[244]	OR 10.5
Germany p,p'-DDT fat levels[245]	Increase
Mexico DDE levels - trend significant[246]	OR 3.8
US Connecticut DDE fat levels[247]	OR 1.5
US Kentucky herbicide area[248].	OR 1.2
US Buffalo NY mirex levels[302]	2.42 bs*
US New York DDE levels[249]	OR 4.0
US North Carolina DDE levels blacks[250]	OR 3.8 bs*
US HCB fat ER+ post-menopausal[251]	OR 7.1
US DDE levels ER+[252]	Increase
US DDE fat levels[253]	Increase
Eye Cancer	
US self reported expos. (uveal melanoma)[33]	OR 1.36 ns
US 4 states[(a)]females in wheat crop areas[251]	Increase
Kidney Cancer	
US 4 sates[(a)] males in wheat crop areas[251]	Increase
Leukemia	
Australia females living sugar cane area[254]	OR 1.54
Canada Quebec live pesticide use area[252]	Increase
Italy flower workers adult children[121]	Increase
Philippines males living rice crop areas[255]	SMR 4.8
US Michigan living pesticide use areas[256]	SIR 1.4
Liver and Biliary Cancer	
US 24 states fat DDE- whites[257]	Increase
US states[(a)] females in wheat crop areas[251]	Increase
Non-Hodgkin Lymphoma	
Australia females living sugar cane area[272]	SMR 1.54
Canada Quebec live pesticide use area[252]	RR 1.6-3.7
Finland chlorophenol water[258]	RR 2.8
Italy men living in rice crop areas[259]	RR 2.07
Women	RR 1.28
US California two fireman[(d)260]	Case report
US Minnesota females in wheat crop areas[261]	SRR 1.35
US Michigan males in pesticide use areas[235]	OR 3.8
Females	OR 1.9
Malignant Melanoma - Skin	
US Georgia pesticide exposure[262]	OR 3.56 bs*
Nasal/Sinonasal Cancer	
Phillippines insecticide coil burning[221]	OR 7.8
US Minnesota females in pesticide areas[279]	SRR 3.35
Ovarian Cancer	
Italy flower workers adult children[121]	SRR 3.35
Italy live corn crop/atrazine use areas[263]	Increase
Italy live corn/herbicide use areas[264]	RR 4.28
Pancreatic Cancer	
Spain DDE levels and K-ras mutatations[265]	OR 8.8
US California DDE serum levels[266]	Increase
US Calif.live hi use county 1,3-dichloropropene[267]	OR 1.89
US Michigan self reported ethylan use[268]	Increase
US 4 states[(a)] living in wheat crop areas[251]	Increase
Prostate Cancer	
Canada Montreal home use[269]	OR 2.3
US 4 states[(a)] males in wheat crop areas[251]	Increase
US Minnesota males in pesticide areas[279]	SRR 1.12 bs*
Rectal Cancer	
US 4 states[(a)] males in wheat crop areas[251]	Increase
Soft Tissue Sarcoma	
Finland chlorophenol water[276]	RR 8.9
Italy men living in rice crop areas[277]	SMR 1.8
Spain men living near HCB[(b)] factory[253]	SIR 5.5
US self-reported herbicide use[195]	OR 2.9
Stomach Cancer	
Hungary males in high pesticide use village[270]	RR 3.20
US 4 states[(a)] living in wheat crop areas[251]	Increase
Thyroid Cancer	
Spain males living near HCB[(b)] factory[253]	SIR 6.7
US 4 states[(a)] males in wheat crop areas[251]	Increase
US Minnesota males in pesticide use areas[279]	SRR 1.12 bs*

* bs = borderline significance

a Minnesota, North Dakota, South Dakota, Montana
b Hexachlorobenzene.
c Hexachlorocyclohexane (lindane)
d Both developed lymphoma 6 years after helping

Table 7
Environmental, Drift, other Non-occupational Pesticide Exposure - Decreased Risk or No Association
(See Appendix F for explanation of the table)

Breast Cancer *(female)*	
Brazil, Rio DDE levels[271]	OR 0.79
Denmark DDT fat levels[272]	No association
Europe[(a)] DDE fat levels[273]	OR 0.48
Germany β-HCH[(b)] fat levels[263]	Decrease
Mexico HCB[(c)] levels[274]	OR 0.46
Norway pesticide[(d)] levels[275]	No association
Sweden DDE fat levels[269]	No association
US California DDT levels[276]	OR 0.90
US Calif. DDE serum levels[277]	No association
US Cape Cod live near cranberry bogs[255]	No association
US Connecticut DDE levels[278]	OR 0.96
US Connecticut oxychlordane[279]	OR 0.7
US Connecticut DDE, DDT fat levels[280]	OR 0.9, 0.8
US Connecticut HCB fat levels [281]	No association
US Connecticut β-HCH[(b)] levels[282]	No association
US Kentucky atrazine exposure[283]	Decrease
US Missouri DDT levels[284]	No association
US North Carolina DDE levels, whites[268]	OR 0.98
US Buffalo NY HCB levels[285]	OR 0.82
US New York DDE serum levels[286]	No association
US New York DDE, transnonachlor[287]	No association
US 24 states DDT fat levels[275]	Decrease
US DDE, DDT tissue levels[288]	No association
US DDE meta-analysis 5 studies[289]	No association
US DDE levels Nurses' Study update[290]	OR 0.82
US DDE1974 serum levels[291]	OR 0.5
US DDE serum levels[292]	OR 0.72
Vietnam DDE/DDT levels[293]	No association
Endometrial Cancer	
Sweden DDE, HCB levels[294]	No association
beta-HCH[(b)]	OR 0.9
US five regions DDE levels[295]	RR 0.7
Liver and Biliary	
US 24 states DDE levels blacks[275]	No association
Non-Hodgkin Lymphoma	
Australia males in sugar cane areas[272]	SMR 0.49
US 24 states DDE fat levels[275]	No association
Multiple Myeloma	
US South Carolina pesticide areas[296]	No association
US 24 states DDE fat levels[275]	No association
Ovarian Cancer	
US Kentucky live atrazine use area[297]	Decrease
Pancreatic Cancer	
US 24 states fat DDE levels[275]	No association
Soft Tissue Sarcoma	
Italy females living in rice crop areas[277]	SMR 0.9
Stomach Cancer	
US California DBCP contamination[298]	No association

a Germany, Netherlands, Northern Ireland, Spain , Switzerland.
b Hexachlorocyclohexane (lindane)
c Hexachlorobenzene
d β-HCH, heptachlor epoxide, oxychlordane, transnonachlor, p,p'-DDE, dieldrin

References:

1. Viel JF, et al. 1995. Bladder cancer among French farmers: does exposure to pesticides in vineyards play a part? Occ Env Med 52(9):587-592.
2. Hours M, et al. 1994. Bladder cancer and occupational exposures. Scand J Work Env Health 20(5):322-330.
3. Daly L, et al. 1994. An investigation of brain tumours and other malignancies in an agricultural research institute. Occ Env Med 51(5):295-298.
4. Alavanja MCR, et al. 1988. Mortality among agricultural extension agents. Am J Ind Med 14:167-176.
5. Blair A, et al. 2002. Mortality among farmers and spouses in the agricultural health study. Ann Epid 12(7):507.
6. Burmeister LF. 1981. Cancer mortality in Iowa farmers, 1971-78. JNCI 66(3):461-464.
7. Saftlas AF, et al. 1987. Cancer and other causes of death among Wisconsin farmers. Am J Ind Med 11:119-129.
8. Ronco G, et al. 1992. Cancer risk among Danish and Italian farmers. Br J Ind Med 49:220-225.
9. Kato I, et al. 1990. An epidemiological study on occupation and cancer risk. Japan J Clin Oncol 20(2):121-127.
10. Morrison HI, et al. 1992. Brain cancer and farming in western Canada. Neuroepidemiology 11(4-6):267-276.
11. Viel JF, et al. 1998. Brain cancer mortality among French farmers: the vineyard pesticide hypothesis. Arch Env Health 53(1):65-70.
12. Corrao G, et al. 1989. Cancer risk in a cohort of licensed pesticide users. Scand J Work Env Hlth 15:203-209.
13. Musicco M, et al. 1982. Gliomas and occupational exposure to carcinogens: case-control study. Am J Epid 116(5):782-790.
14. Reif JS, et al. 1989. Occupational risks for brain cancer: a New Zealand Cancer Registry-based study. J Occ Med 31(10):863-867.
15. Kristensen P, et al. 1996. Incidence and risk factors of cancer among men and women in Norwegian agriculture. Scand J Work Env Health 22(1):14-26.
16. Heineman EF, et al. 1995. Occupational risk factors for brain tumors among women in Shanghai, China. J Occ Env Med 37(3):288-293.
17. Navas-Acien A, et al. 2002. Occupation, exposure to chemicals and risk of gliomas and meningiomas in Sweden. Am J Ind Med 42(3):214-227.
18. Mills PK, et al. 2001. Cancer incidence in the United Farmworkers of America (UFW), 1987-1997. Am J Ind Med 40(5):596-603.
19. Stubbs HA, et al. 1984. A proportionate mortality analysis of California agricultural workers, 1978-1979. Am J Ind Med 6:305-320.
20. Khuder SA, et al.1998. Meta-analyses of brain cancer and farming. Am J Ind Med 34(3):252-260.
21. Brownson RC, et al. 1990. An analysis of occupational risks for brain cancer. Am J Publ Hlth 80(2):169-72.
22. Cocco P, et al. 1999. Occupational risk factors for cancer of the central nervous system (CNS) among US women. Am J Ind Med 36(1):70-74.
23. Blair A, et al. 1993. Cancer and other causes of death among male and female farmers from twenty-three states. Am J Ind Med 23(5):729-742.
24. Lee E, et al. 2002. Proportionate mortality of crop and livestock farmers in the United States, 1984-1993. Am J Ind Med 42(5):410-420.
25. Band PR, et al. 2000. Identification of occupational cancer risks in British Columbia. A population-based case-control study of 995 incident breast cancer cases by menopausal status, controlling for confounding factors. J Occ Env Med 42(3):284-310.

26. Brophy JT, et al.2002. Occupational histories of cancer patients in a Canadian cancer treatment center and the generated hypothesis regarding breast cancer and farming. Int J Occ Env Hlth 8(4):346-353.
27. Kocic B, et al. 1996. [Some insufficiently recognized risk factors for breast cancer]. Srp Arh Celok Lek 124(7-8):175-178.
28. Duell EJ, et al. 2001. Reproducibility of reported farming activities and pesticide use among breast cancer cases and controls. A comparison of two modes of data collection. Ann Epid 11(3):178-185.
29. Zhong Y, et al. 1996. Cancer incidence among Icelandic pesticide users. Int J Epid 25(6):1117-1124.
30. Forastiere F, et al. 1993. Cancer among farmers in central Italy. Scand J Work Hlth Env 10(6):382-389.
31. Alavanja MCR, et al. 1989. Mortality among forest and soil conservationists. Arch Env Health 44:94-101.
32. Keller JE, et al. 1994. Case-control studies of cancer in Illinois farmers using data from the Illinois State Cancer Registry and the U.S. Census of Agriculture. Eur J Can 30A(4):469-473.
33. Ajani UA, et al 1992. Occupation and risk of uveal melanoma. An exploratory study. Cancer 70(12):2891-2900.
34. Franceschi S, et al. 1991. Occupation and risk of Hodgkin's disease in north-east Italy. Int J Can 48(6):831-835.
35. LaVecchia C, et al. 1989. Occupation and lymphoid neoplasms. Br J Can 60:385-388.
36. Hu J, et al. 2002. Renal cell carcinoma and occupational exposure to chemicals in Canada. Occ Med 52:157-164 .
37. Mellemgaard A, et al. 1994. Occupational risk factors for renal-cell carcinoma in Denmark. Scand J Work Env Health 20(3):160-165.
38. Buzio L, et al. 2002. Occupational risk factors for renal cell cancer. An Italian case-control study. Med Lav 93(4):303-309.
39. Gallagher RP, et al. 1984. Cancer and aplastic anemia in British Columbia farmers. JNCI 72(6):1311-1315.
40. Hansen ES, et al.1992. A cohort study on cancer incidence among Danish gardeners. Am J Ind Med 21(5):651-660.
41. Viel JF, et al. 1993. Lymphoma, multiple myeloma and leukaemia among French farmers in relation to pesticide exposure. Soc Sci Med 37(6):771-777.
42. Richardson S, et al. 1992. Occupational risk factors for acute leukaemia: a case-control study. Int J Epid 21(6):1063-1073.
43. Sperati A, et al. 1999. Mortality among male licensed pesticide users and their wives. Am J Ind Med 36(1):142-146.
44. Assennato G, et al. 1997. [Hemo-lymphopoietic tumors in agriculture. Case-control study in an epidemiologic area of southern Bari]. G Ital Med Lav Ergon 19(1):26-29.
45. Nanni O, et al. 1996. Chronic lymphocytic leukemias and non-Hodgkin's lymphomas by histological type in farming-aminal breeding workers: a population case-control study based on a priori exposure matrices. Occ Env Med 53:652-657.
46. Amadori D, et al. 1995. Chronic lymphocytic leukemias and non-Hodgkin's lymphomas by histological type in farming-animal breeding workers: a population case-control study based on job titles. Occ Env Med 52:374-379.
47. Ciccone G, et al. 1993. Myeloid leukemias and myelodysplastic syndromes: chemical exposure, histologic subtype and cytogenetics in a case-control study. Can Genet Cytogenet 68(2):135-139.
48. Pearce NE, et al. 1986. Leukemia among New Zealand agricultural workers. A cancer registry-based study. Am J Epid 124:402-409.
49. Linet MS, et al. 1994. Occupation and hematopoietic and lymphoproliferative malignancies among women: a linked registry study. J Occ Med 36(11):1187-1198.
50. Flodin U, et al. 1988. Chronic lymphatic leukemia and engine exhausts, fresh wood, and DDT: a case-referent study. Br J Ind Med 45:33-38.
51. Cantor KP, et al. 1999. Mortality among aerial pesticide applicators and flight instructors: follow-up from 1965-1988. Am J Ind Med 36(2):239-247.
52. Alavanja MCR, et al. 1990. Cancer mortality in the U.S. flour industry. JNCI 82:840-848.
53. Burmeister LF, et al. 1982. Leukemia and farm practices in Iowa. Am J Epid 115(5):720-728.
54. Brown LM, et al. 1990. Pesticide exposures and other agricultural risk factors for leukemia among men in Iowa and Minnesota. Can Res 50:6585-6591.
55. Blair A, et al. 1985. Leukemia and farm practices. Am J Epid 122:535.
56. Everett G, et al. 1985. Environmental chemical exposures as risk factors for leukemia and non-Hodgkins's lymphoma (abstract). Am J Epid 122(3):535-536.
57. Blair A, et al. 1979. Leukemia among Nebraska farmers: a death certificate study. Am J Epid 110(3):264-273.
58. Delzell W, et al. 1985. Mortality among white and nonwhite farmers in North Carolina, 1976-1978. Am J Epid 121(3):391-402.
59. Gallagher RP, et al. 1985. Cancer mortality experience of woodworkers, loggers, fisherman, farmers, and miners in British Columbia. NCI Monograph 69:163-167.
60. Alavanja MCR, et al. 1987. Occupational cancer risk associated with the storage and bulk handling of agricultural foodstuff. J Toxicol Env Health 22(3)247-254.
61. Stemhagen A, et al. 1983. Occupational risk factors and liver cancer. Am J Epid 117(4):443-454.
62. Austin H, et al. 1987. Case-control study of hepato-cellular carcinoma, occupation and chemical exposures. J Occ Med 29:665-69.
63. McDuffie HH, et al. 1988. Farming and exposure to chemicals in male lung cancer patients and their siblings. J Occ Med 30:55-59.
64. Levin LI, et al. 1988. Occupation and lung cancer in Shanghai: a case-control study. Br J Ind Med 45(7):450-458.
65.Chan-Yeung M, et al. 2003. Risk factors associated with lung cancer in Hong Kong. Lung Cancer 40(2):131-140.
66. Brownson RC, et al. 1993. Occupational risk factors for lung cancer among nonsmoking women: a case-control study in Missouri (United States). Can Causes Contr 4(5):449-454.
67. Green A, et al. 1999. A case-control study of melanomas of the soles and palms (Australia and Scotland). Can Causes Contr 10(1):21-25.
68. Wesseling C, et al. 1996. Cancer in banana plantation workers in Costa Rica. Int J Epid 25(6):1125-1131.
69. Wiklund K, et al. 1995. Cancer risks among male farmers in Sweden. Eur J Can Prev 4(1):81-90.
70. Semenciw RM, et al. 1993. Multiple myeloma mortality and agricultural practices in the prairie provinces of Canada. J Occ Med 35:557-561.
71. Cuzick J, et al. 1988. Multiple myeloma – a case-control study. Br J Can 57(5):516-520.
72. Franceschi S, et al. 1993. Cancer risk in farmers: results from a multi-site case-control study in North-Eastern Italy. Int J Can 53(5):740-745.
73. Nanni O, et al. 1998. Multiple myeloma and work in agriculture: results of a case-control study in Forli, Italy. Can Causes Contr 9(3):277-283.
74. Eriksson M, et al. 1992. Occupational and other environmental factors and multiple myeloma: a population based case-control study. Br J Ind Med 49(2):95-103.
75. McLaughlin J, et al. 1988. Multiple myeloma and occupation in Sweden. Arch Env Health 43:7-10.
76. Wiklund, K. 1986. Trends in cancer risks among Swedish agricultural workers. JNCI 77(3):657-664.
77. Boffetta P, et al. 1989. A case-control study of multiple myeloma nested in the American Cancer Society prospective study. Int J Can 43(4):554-549.
78. Cantor KP, et al. 1984. Farming and mortality from multiple myeloma: a case-control study with the use of death certificates. JNCI 72(2):251-255.
79. Morris PD, et al. 1986. Toxic substance exposure and multiple myeloma: a case-control study. JNCI 76(6):987-994.

80. Demers PA, et al. 1993. A case-control study of multiple myeloma and occupation. Am J Ind Med 23(4):629-639.
81. Khuder SA, et al. 1997. Meta-analyses of multiple myeloma and farming. Am J Ind Med 32(5):510-516.
82. Olsen JH. 1988. Occupational risks of sinonasal cancer in Denmark. Br J Ind Med 45(5):329-335.
83. Leclerc A, et al. 1997. Sinonasal cancer and occupation. Results from the reanalysis of 12 case-control studies. Am J Ind Med 31(2):153-65.
84. Luce D, et al. 1992. Occupational risk factors for sinonasal cancer: a case control study in France. Am J Ind Med 21:163-175.
85. Wiklund K, et al. 1988. Cancer in the respiratory organs of Swedish farmers. Cancer 61(5):1055-1058.
86. Fleming LE, et al. 2003. National Health Interview Survey mortality among US farmers and pesticide applicators. Am J Ind Med 43(2):227-233.
87. Cocco P, et al. 1999. Occupational risk factors for cancer of the central nervous system (CNS) among US women. Am J Ind Med 36(1):70-74.
88. Partanen T, et al. 1994. Pancreatic cancer in industrial branches and occupations in Finland. Am J Ind Med 25(6):851-866.
89. Alguacil J, et al. 2000. Risk of pancreatic cancer and occupational exposures in Spain. Ann Occ Hyg 44(5):391-403.
90. Alavanja MCR, et al. 1987. Proportionate mortality study of workers in the grain industry. JNCI 78(2):247-252.
91. Falk RT, et al. 1990. Occupation and pancreatic cancer risk in Louisiana. Am J Ind Med 18:565-576.
92. Ji BT, et al. 2001. Occupational exposure to pesticides and pancreatic cancer. Am J Ind Med 39(1):92-99.
93. Morrison HI, et al. 1993. Farming and prostate cancer mortality. Am J Epid 137(3):270-280.
94. Fincham SM, et al. 1992. Patterns and risks of cancer in farmers in Alberta. Cancer 69:1276-1285.
95. Inskip H, et al. 1996. Mortality of farmers and farmers' wives in England and Wales 1979-80, 1982-90. Occ Env Med 53(11):730-735.
96. Settimi L, et al. 2001. Cancer risk among male farmers: a multi-site case-control study. Int J Occ Med Env Hlth 14(4):339-347.
97. Settimi L, et al. 2003. Prostate cancer and exposure to pesticides in agricultural settings. Int J Cancer 104(4):458-461.
98. VanDerGulden JW, et al. 1995. Work environment and prostate cancer risk. Prostate 27(5):250-257.
99. Dich J, et al. 1998. Prostate cancer in pesticide applicators in Swedish agriculture. Prostate 34(2):100-112.
100. Brownson RC, et al. 1989. Cancer risks among Missouri farmers. Cancer 64:2381-2386.
101. Keller JE, et al. 1994. Case-control studies of cancer in Illinois farmers using data from the Illinois State Cancer Registry and the U.S. Census of Agriculture. Eur J Can 30A(4):469-473.
102. Alavanja MCR, et al. 2003. Use of agricultural pesticides and prostate cancer risk in the Agricultural Health Study cohort. Am J Epid 157:800-814.
103. Potti A, et al. 2003. Prevalence of pesticide exposure in young males (≤50 years) with adenocarcinoma of the prostate. J Carcinog 2(1):4.
104. Dosemeci M, et al. 1994. Farming and prostate cancer among African-Americans in the Southeastern United States. JNCI 86(22):1718-1719.
105. Wingren G, et al, 1990. Soft tissue sarcoma and occupational exposures. Cancer 66(4):806-811.
106. Zahm SH, et al. 1988. A case-referent study of soft-tissue sarcoma and Hodgkin's disease; farming and insecticide use. Scand J Work Env Health 14:224-230.
107. Cocco P, et al. 1994. Occupational exposures as risk factors for gastric cancer in Italy. Can Causes Contr 5(3):241-248.
108. Burns PB, et al. 1995. Stomach cancer risk among black and white men and women: the role of occupation and cigarette smoking. J Occ Env Med 37(10):1218-1223.
109. Colt JS, et al. 2001. Proportionate mortality among US migrant and seasonal farm workers in twenty-four states. Am J Ind Med 40(5):604-611.
110. McDowall M, et al. 1986. Testicular cancer mortality in England and Wales 1971-80: variations by occupation. J Epid Com Hlth 40:26-29.
111. McDowall M, et al. 1984. Testicular cancer and employment in agriculture (letter). Lancet 1:510-511.
112. Hardell L, et al. 1998. Case-control study on risk factors for testicular cancer. Int J Oncol 13(6):1299-1303.
113. Wiklund, K. 1986. Testicular cancer among agricultural workers and licensed pesticide applicators in Sweden. Scand J Work Hlth Env 12:630-631.
114. Brown LM, et al. 1984. Testicular cancer and farming . Lancet 1:1356.
115. Mills PK, et al. 1984. Testicular cancer associated with employment in agricultural and oil and natural gas extraction. Lancet 1:207-209.
116. McDuffie HH, et al. 2002. Canadian male farm residents, pesticide safety handling practices, exposure to animals and non-Hodgkin's lymphoma (NHL). Am J Ind Med Suppl 2:54-61.
117. McDuffie HH, et al. 2001. Non-Hodgkin's lymphoma and specific pesticide exposures in men: cross-Canada study of pesticides and health. Can Epid Biomark Prev 10(11):1155-1163.
118. Mao Y, et al. 2000. Non-Hodgkin's lymphoma and occupational exposure to chemicals in Canada. Ann Oncol 11(Suppl 1):69-73.
119. Morrison HI, et al. 1994. Non-Hodgkin's lymphoma and agricultural practices in the prairie provinces of Canada. Scand J Work Env Health 20(1):42-47.
120. Wigle DT, et al. 1990. Mortality study of Canadian male farm operators: non-Hodgkin's lymphoma mortality and agricultural practices in Saskatchewan. JNCI 82(7):575-582.
121. Clavel J, et al. 1996. Farming, pesticide use and hairy-cell leukemia. Scan J Work Env Health 22(4):285-293.
122. Clavel J, et al. 1995. Hairy cell leukaemia, occupation, and smoking. Br J Haematol 91(1):154-161.
123. Betta PG, et al. 1994. Triazine herbicides and non-Hodgkin's lymphomas (NHL). A case-control study. Proc Annu Meet Am Soc Clin Oncol 13:A534.
124. Pearce NE, et al. 1987. Non-Hodgkin's lymphoma and farming. An expanded case-control study, Int J Can 39:155-161.
125. Pearce NE, et al. 1985. Malignant lymphoma and multiple myeloma linked with agricultural occupations in a New Zealand cancer registry-based study. Am J Epid 121(2):225-237.
126. Hardell L, et al. 2002. Exposure to pesticides as risk factor for non-Hodgkin's lymphoma and hairy cell leukemia: pooled analysis of two Swedish case-control studies. Leuk Lymph 43(5):1043-1049.
127. Nordstrom M, et al. 1998. Occupational exposures, animal exposure and smoking as risk factors for hairy cell leukaemia evaluated in a case-control study. Br J Can 77(11):2048-2052.
128. Linet MS, et al. 1993. Non-Hodgkin's lymphoma and occupation in Sweden: a registry based analysis. Br J Ind Med 50:79-84.
129. Cantor K, et al. 1985. Farming and non-Hodgkin's lymphoma. Am J Epid 122(3):535.
130. Baris D, et al. 1998. Agricultural use of DDT and risk of non-Hodgkin's lymphoma: Pooled analysis of three case-control studies in the United States.Occ Env Med 55(8):522-527.
131. Figgs LW, et al. 1995. United States non-Hodgkin's lymphoma surveillance by occupation 1984-1989: a twenty-four state death certificate study. Am J Ind Med 27(6):817-835.
132. Waddell BL, et al. 2001. Agricultural use of organophosphate pesticides and the risk of non-Hodgkin's lymphoma among male farmers (United States). Can Causes Contr 12(6):509-517.
133. Keller-Byrne JE, et al. 1997. A meta-analyses of non-Hodgkin's lymphoma among farmers in the central United States. Am J Ind Med 31(4):442-444.

134. Khuder SA, et al. 1998. Meta-analyses of non-Hodgkin's lymphoma and farming. Scand J Work Env Health 24(4):255-261.
135. Buesching DP, et al. 1984. Cancer mortality among farmers. JNCI 72:503-504.
136. Burmeister LF, et al. 1982. Selected cancer mortality and farm practices in Iowa. Am J Epid 118(1):72-77.
137. Folsom AR, et al. 1996. Cancer incidence among women living on farms: findings from the Iowa women's health study. J Occ Env Med 38(11):1171-1176.
138. Cantor K, et al. 1985. Farming and non-Hodgkin's lymphoma. Am J Epid 122(3):535.
139. Hoar SK, et al. 1986. Agricultural herbicide use and risk of lymphoma and soft-tissue sarcoma. JAMA 256(9):1141-1147.
140. Zahm SH, et al. 1993. The role of agricultural pesticide use in the development of non-Hodgkin's lymphoma in women. Arch Env Health 48(5):353-358.
141. Weisenburger DD. 1990. Environmental epidemiology of non-Hodgkin's lymphoma in eastern Nebraska. Am J Ind Med 18(3):303-305.
142. Zahm SH, et al. 1990. A case-control study of non-Hodgkin's lymphoma and the herbicide 2,4-dichlorophenoxyacetic acid (2,4-D) in Eastern Nebraska. Epidemiology 1:349-356.
143. Woods JS, et al. 1987. Soft tissue sarcoma and non-Hodgkin's lymphoma in relation to phenoxyherbicide and chlorinated phenol exposure in western Washington. JNCI 78(5):899-910.
144. Cantor KP. 1982. Farming and mortality from non-Hodgkin's lymphoma: a case-control study. Int J Can 29:239-248.
145. Menegoz F, et al. 2002. Contacts with animals and humans as risk factors for adult brain tumours. An international case-control study. Eur J Can 38(5):696-704.
146. Schiff D, et al. 1998. Risk factors for primary central nervous system lymphoma: a case-control study. Cancer 82(5):975-982.
147. Duell EJ, et al. 2000. A population-based case-control study of farming and breast cancer in North Carolina. Epidemiology 11(5):523-531.
148. Tollestrup K, et al. 1995. Mortality in a cohort of orchard workers exposed to lead arsenate pesticide spray. Arch Env Health 50(3):221-229.
149. Chow WH, et al. 1994. Occupation and stomach cancer in a cohort of Swedish men. Am J Ind Med 26(4):511-520.
150. Spinelli JJ, et al. 1996. Hodgkins Disease (HD) and pesticide exposure. Epidemiology 7(4):S59.
151. Torchio P, et al. 1994. Mortality study on a cohort of Italian licensed pesticide users. Sci Total Env 149(3):183-191.
152. Partanen T, et al. 1991. Renal cell cancer and occupational exposure to chemical agents. Scand J Work Env Health 17(4):231-239.
153. Wiklund K, et al. 1989. Risk of cancer in pesticide applicators in Swedish agriculture. Br J Ind Med 46(11):809-814.
154. Semenciw RM, et al. 1994. Leukemia mortality and farming in the prairie provinces of Canada. Can J Pub Hlth 85(3):208-211.
155. Loomis DP, et al. 1991. Occupation and leukemia mortality among men in 16 states: 1985-1987. Am J Ind Med 19:509-552.
156. Algranti E, et al. 2001. Lung cancer in Brazil. Semin Oncol 28(2):143-152.
157. Wicklund KG, et al. 1988. Respiratory cancer among orchardists in Washington State, 1968 to 1980. J Occ Med 30(7):561-564.
158. Fritschi L, et al. 1996. Lymphoma, myeloma and occupation: results of a case-control study. Int J Can 67(4):498-503.
159. Franceschi S, Serraino D, Bidoli E; et al. 1989. The epidemiology of non-Hodgkin's lymphoma in the north-east of Italy: a hospital-based case-control study. Leuk Res 13(6):465-472.
160. Schumacher MC, et al. 1988. A death-certificate case-control study of non-Hodgkin's lymphoma and occupation in men in North Carolina. Am J Ind Med 13(3):317-330.
161. Parker AS, et al. 1999. A cohort study of farming and risk of prostate cancer in Iowa. Epidemiology 10(4):452-455.
162. Cantor KP, et al. 1991. Mortality among aerial pesticide applicators and flight instructors: a reprint. Arch Env Health 46(2):110-116.
163. Kilpatrick R, et al.1987. Mortality from soft tissue sarcomas in agricultural workers (1972-1981). Chemosphere 16(8/9):2101-2106.
164. Serraino D, et al. 1992. Occupation and soft-tissue sarcoma in northeastern Italy. Can Causes Contr 3(1):25-30.
165. Vineis P, et al. 1986. Phenoxy herbicides and soft-tissue sarcomas in female rice weeders: A population-based case-referent study. Scand J Work Env Hlth 13:9-17.
166. Knight JA et al. 1996. Occupation and risk of germ cell testicular cancer by histological type in Ontario. J Occ Env Med 38(9):884-890.
167. VanDenEden SK, et al. 1991. Occupation and the occurrence of testicular cancer. Am J Ind Med 19:327-337.
168. Carstensen JM, et al. 1990. Occupational risks of thyroid cancer: data from the Swedish cancer-environment register, 1961-1979. Am J Ind Med 18(5):535-540.
169. Thomas HF, et al. 1996. Cancer mortality among local authority pest control officers in England and Wales. Occ Env Med 53(11):787-790.
170. Wang HH, et al. 1979. Mortality of pesticide applicators. J Occ Med 21(11):741-744.
171. Figa-Talamanca, et al. 1993. Mortality in a cohort of pesticide applicators in an urban setting. Int J Epid 22(4):674-675.
172. Kross BC, et al. 1996. Proportionate mortality study of golf course superintendents. Am J Ind Med 29(5):501-506.
173. Beard J, et al. 2003. Health impacts of pesticide exposure in a cohort of outdoor workers. Env Health Persp 111(5):724-730.
174. Cocco P, et al. 1997. Long-term health effects of the occupational exposure to DDT. A preliminary report. Ann N Y Acad Sci 837:246-256.
175. Pesatori AC, et al. 1994. Cohort mortality and nested case-control study of lung cancer among structural pest control workers in Florida (United States). Can Causes Contr 5(4):310-318.
176. MacMahon BB, et al. 1988. A second follow-up of mortality in a cohort of pesticide applicators. J Occ Med 30(5):429-432.
177. Zahm SH. 1997. Mortality study of pesticide applicators and other employees of a lawn care service company. J Occ Env Med 39(11):1055-1067.
178. Swaen GMH, et al. 1992. Cancer mortality among licensed herbicide applicators. Scand J Work Hlth Env18:201-204.
179. Fleming LE, et al. 1999. Cancer incidence in a cohort of licensed pesticide applicators in Florida. J Occ Env Med 41(4):279-288.
180. Saracci R, et al. 1991. Cancer mortality in workers exposed to chlorophenoxy herbicides and chlorophenols. Lancet 338(8774):1027-1032.
181. Asp S, et al. 1994. Mortality and cancer morbidity of Finnish chlorophenoxy herbicide applicators: an 18-year prospective follow-up. Am J Ind Med 26(2):243-253.
182. Wiklund K, et al. 1988. Soft tissue sarcoma risk in Swedish licensed pesticide applicators. J Occ Med 30(10):801-804.
183. Popp W, et al. 1992. Incidence of bladder cancer in a cohort of workers exposed to 4-chloro-o-toluidine while synthesizing chlordimeform. Br J Ind Med 49:529-531.
184. Brown DP. 1992. Mortality of workers employed at organochlorine pesticide manufacturing plants - an update. Scand J Work Env Hlth 18:155-161.
185. Zahm SH, et al. 1987. The National Bladder Cancer Study: employment in the chemical industry. JNCI 79(2):217-222.
186. Manz A, et al. 1991. Cancer mortality among workers in chemical plant contaminated with dioxin. Lancet 338:959-964.
187. Kogevinas M, et al. 1993. Cancer incidence and mortality in women occupationally exposed to chlorophenoxy herbicides, chlorophenols, and dioxins. Can Causes Contr 4(6):547-553.
188. Norman SA, et al. 1995. Cancer incidence in a group of workers potentially exposed to ethylene oxide. Int J Epid 24(2):276-284.

189. Leet T, et al. 1996. Cancer incidence among Alachlor manufacturing workers. Am J Ind Med 30(3):300-306.
190. Mabuchi K et al. 1980. Cancer and occupational exposure to arsenic: A study of pesticide workers. Prev Med 9:51-77.
191. Holly EA, et al. 1996. Intraocular melanoma linked to occupations and chemical exposures. Epidemiology 7:55-61.
192. Persson B, et al. 1993. Some occupational exposures as risk factors for malignant lymphomas. Cancer 72(5):1773-1778.
193. Kogevinas M, et al. 1997. Cancer mortality in workers exposed to phenoxy herbicides, chlorophenols, and dioxins. An expanded and updated international cohort study. Am J Epid 145(12):1061-1075.
194. Ramlow JM, et al. 1996. Mortality in a cohort of pentachlorophenol manufacturing workers, 1940-1989. Am J Ind Med 30(2:):180-194.
195. Coggon D, et al. 1986. Mortality of workers exposed to 2 methyl-4 chlorophenoxyacetic acid. Scand J Work Env Hlth 12:448-454.
196. Hagmar et al. 1995. Cancer incidence in Swedish sterilant workers exposed to ethylene oxide. Occ Env Med 52(3):154-156.
197. Coggon D, et al. 1991. Mortality and incidence of cancer at four factories making phenoxy herbicides. Br J Ind Med 48:173-178.
198. Checkoway H, et al. 1996. Reanalysis of mortality from lung cancer among diatomaceous earth industry workers, with considerations of potential confounding by asbestos exposure. Occ Env Med 53:645-647.
199. Olsen GW, et al. 1995. Update of the mortality experience of employees with occupational exposure to 1,2-dibromo-3-chloropropane (DBCP). Am J Ind Med 28(3):399-410.
200. DiTraglia DP. 1990. Mortality study of pesticide manufacturers formulators: documentation of the Velsicol Chemical Company, in Memphis, Tennessee cohort . NIOSH, Contract No. 210-76-0173.
201. Wong O, et al. 1984. Mortality of workers potentially exposed to organic and inorganic brominated chemicals, DBCP, TRIS, PBB and DDT. Br J Ind Med 41:15-25.
202. Luc D, et al. 2002. Sinonasal cancer and occupational exposures: a pooled analysis of 12 case-control studies. Can Causes Contr 13(2):147-157.
203. West S, et al. 1993. Non-viral risk factors for nasopharyngeal carcinoma in the Philippines: results from a case-control study. Int J Can 55(5):722-727.
204. Zhu K, et al. 2002. Case-control study evaluating the homogeneity and heterogeneity of risk factors between sinonasal and nasopharyngeal cancers. Int J Can 99(1):119-123.
205. Mirabelli MC, et al. 2000. Occupational exposure to chlorophenol and the risk of nasal and nasopharyngeal cancers among U.S. men aged 30 to 60. Am J Ind Med 37(5):532-541.
206. Becher H, et al. 1996. Cancer mortality in German male workers exposed to phenoxy herbicides and dioxins. Can Causes Contr 7(3):312-321.
207. Hardell L, et al. 1994. Exposure to phenoxyacetic acids chlorophenols or organic solvents in relation to histopathology, stage, and anatomical localization of non-Hodgkin's lymphoma. Can Res 54(9):2386-2389.
208. Acquavella JF, et al. 1996. Evaluation of mortality and cancer incidence among Alachlor manufacturing workers. Env Health Persp 104(7):728-733.
209. Wong O, et al. 1993. An epidemiological study of workers potentially exposed to ethylene oxide Br J Ind Med. 50(4):308-316.
210. Kernan GJ, et al. 1999. Occupational risk factors for pancreatic cancer: a case-control study based on death certificates from 24 U.S. states. Am J Ind Med 36(2):260-270.
211. Garabrant DH, et al. 1992. DDT and related compounds and risk of pancreatic cancer. JNCI 84:764-771.
212. Cocco P, et al. 1998. Mortality from cancer of the male reproductive tract and environmental exposure to the anti-androgen p,p'-dichlorodiphenyldichloroethylene in the United States. Oncology 55(4):334-339.
213. Hoppin JA, et al. 1999. Occupational risk factors for sarcoma subtypes. Epidemiology 10(3):300-306.
214. Hardell L, et al. 1988. The association between soft-tissue sarcomas and exposure to phenoxyacetic acids. A new case-referent study. Cancer 62:652-656.
215. Kogevinas M, et al. 1995. Soft tissue sarcoma and non-Hodgkin's lymphoma in workers exposed to phenoxy herbicides, chlorophenols, and dioxins: two nested case-control studies. Epidemiology 6(4):396-402.
216. Lynge, E. 1993. Cancer in phenoxy herbicide manufacturing workers in Denmark, 1947-87 – an update. Can Causes Contr 4(3):261-272.
217. Sathiakumar N, et al. 1992. A follow-up study of agricultural chemical production workers. Am J Ind Med 21(3):321-330.
218. Eriksson M, et al. . 1990. Exposure to dioxins as risk factor for soft tissue sarcoma: a population-based case-control study. JNCI 82:486-490.
219. Eriksson M, et al. 1981. Soft-tissue sarcomas and exposure to chemical substances: a case-referent study. Br J Ind Med 38:27-33.
220. Smith AH, et al. 1984. Soft tissue sarcoma and exposure to phenoxy herbicides and chlorophenols in New Zealand. JNCI 73:1111-1117.
221. Ekstrom AM, et al. 1999. Occupational exposures and risk of gastric cancer in a population-based case-control study. Can Res 59(23):5932-5937.
222. Wiklund K, et al. 1988. Risk of tumors of the nervous system among mercury and other seed disinfectant appplicators in Swedish agriculture. Acta Oncologica 27(6b):865.
223. Cocco P, et al. Case-control study of occupational exposures and male breast cancer. Occ Env Med 55(9):599-604.
224. Gardner MJ, et al. 1989. Workers exposed to ethylene oxide: a follow up study. Br J Ind Med 46(12):860-865.
225. Kiesselbach N, et al. 1990. A multicentre mortality study of workers exposed to ethylene oxide. Br J Ind Med 47:182-188.
226. DeJong G, et al. 1997. Mortality of workers exposed to dieldrin and aldrin: A retrospective cohort study. Occ Env Med 54(10):702-707.
227. Shindell S, et al. 1986. Mortality of workers employed in the manufacture of Chlordane: An update. J Occ Med 28(7):4987-4501.
228. Hardell L, et al. 1999. A case-control study of non-Hodgkin lymphoma and exposure to pesticides. Cancer 85(6):85:1353-1360.
229. Teta MJ, et al. 1993. Mortality study of ethylene oxide workers in chemical manufacturing: a 10 year update. Br J Ind Med 50(8):704-709.
230. Teta MJ, et al. 1999. Ethylene oxide cancer risk assessment based on epidemiological data: application of revised regulatory guidelines. Risk Anal 19(6):1135-1155.
231. BuenoDeMesquita HB, et al. 1993. Occupational exposure to phenoxy herbicides and chlorophenols and cancer mortality in The Netherlands. Am J Ind Med 23(2):289-300.
232. Cantor KP, et al. 1987. Bladder cancer, drinking water source, and tap water consumption: a case-control study. JNCI 79(6):1269-1279.
233. Schreinemachers DM. 2000. Cancer mortality in four northern wheat-producing states. Env Hlth Persp 108(9):873-881.
234. Godon D, et al. 1989. [Pesticides and cancer in a Quebec rural farming population: a geographical interpretation.] Soc Sci Med 29(7):819-833.
235. Grimalt JO, et al. 1994. Risk excess of soft-tissue sarcoma and thyroid cancer in a community exposed to airborne organochlorinated compound mixtures with a high hexachlorobenzene content. Int J Can 56(2):200-203.
236. Ahlbom A, et al. 1986. Nonoccupational risk indicators for astrocytomas in adults. Am J Epid 124(2):334-337.
237. Aschengrau A, et al. 1996. Cancer risk and residential proximity to cranberry cultivation in Massachusetts. Am J Publ Hlth 86(9):1289-1296.
238. Demers A, et al. 2000. Risk and aggressiveness of breast cancer in relation to plasma organochlorine concentrations. Can Epid Biomark Prev 9(2):161-166.

239. Woolcott CG, et al. 2001. Organochlorines and breast cancer risk by receptor status, tumor size, and grade (Canada). Can Causes Cont 12(5):395-404.
240. Desi I, et al. 1998. Epidemiological investigations and experimental model studies on exposure of pesticides. Organochlorine exposure and breast cancer risk in Colombian women. Toxicol Lett 14(Suppl 3):125-132.
241. Hoyer AP, et al. 2000. Organochlorine exposure and breast cancer survival. J Clin Epidemiol 53(3):323-330.
242. Hoyer AP, et al. 2000. Repeated measurements of organochlorine exposure and breast cancer risk (Denmark). Can Causes Contr 11(2):177-184.
243. Hoyer AP, et al. 1998. Organochlorine exposure and risk of breast cancer. Lancet 352:1816-1820.
244. Mussalo-Rayganaam H, et al. 1990. Occurrence of β-hexachlorocyclohexane in breast cancer patients. Cancer 66:2124-2148.
245. Guttes S, et al. 1998. Chlororganic pesticides and polychlorinated biphenyls in breast tissue of women with benign and malignant breast disease. Arch Env Contam Toxicol 35(1):140-147.
246. Romieu Iet al. 2000. Breast cancer, lactation history, and serum organochlorines. Am J Epid 152(4):363-370.
247. Falck FJr, et al. 1992. Pesticides and polychlorinated biphenyl residues in human breast lipids and their relation to breast cancer. Arch Env Health 47:143-146.
248. Kettles MK, et al. 1997. Triazine herbicide exposure and breast cancer incidence: an ecologic study of Kentucky counties. Env Hlth Persp 105(11):1222-1227.
249. Wolff MS, et al. 1993. Blood levels of organochlorine residues and risk of breast cancer. JNCI 85(8):648-652.
250. Millikan R, et al. 2000. Dichlorodiphenyldichloroethene, polychlorinated biphenyls, and breast cancer among African-American and white women in North Carolina. Can Epid Biomark Prev 9(11):1233-1240.
251. Liljegren G, et al. 1998. Case-control study on breast cancer and adipose tissue concentrations of congener specific polychlorinated biphenyls, DDE and hexachlorobenzene. Eur J Can Prev 7(2):135-140.
252. Dewailly E, et al. 1994. High organochlorine body burden in women with estrogen receptor-positive breast cancer. JNCI 86(3):232-234.
253. Djordjevic MV, et al. 1994. Assessment of chlorinated pesticides and polychlorinated biphenyls in adipose breast tissue using a supercritical fluid extraction method. Carcinogenesis 15(11):2581-2585.
254. McCabe M, et al. 1984. Cancer of lymphatic tissues in cane-growing areas of Queensland. Med J Aust 141(7):412-414.
255. Loevinsohn ME. 1987. Insecticide use and increased mortality in rural central Luzon, Phillipines. Lancet 1:1359-1362.
256. Waterhouse D, et al. 1996. Cancer incidence in the rural community of Tecumseh, Michigan: a pattern of increased lymphopoietic neoplasms. Cancer 77(4):763-770.
257. Cocco P, et al. 2000. Cancer mortality and environmental exposure to DDE in the United States. Env Health Persp 108(1):1-4.
258. Lampi P, et al. 1992. Cancer incidence following chlorophenol exposure in a community in southern Finland. Arch Env Health 47(3):167-175.
259. Vineis P, et al. 1991. Incidence rates of lymphomas and soft-tissue sarcomas and environmental measurements of phenoxy herbicides. JNCI 83(5):362-363.
260. Markovitz A, et al. 1984. Chemical carcinogenesis: a soil fumigant, 1,3-dichloropropene as possible cause of hematologic malignancies. Arch Int Med 144:1409-1411.
261. Schreinemachers DM, et al. 1999. Cancer mortality in agricultural regions of Minnesota. Env Hlth Persp 107(3):205-211.
262. Hicks N, et al. 1985. Life-style factors among patients with melanoma. South Med J 78(8):903-908.
263. Donna A, et al. 1989. Triazine herbicides and ovarian epithelial neoplasms. Scand J Work Env Health 15:47-53.
264. Donna A, et al. 1984. Ovarian mesothelial tumors and herbicides: a case-control study. Carcinogenesis 5:941-942.
265. Porta M, et al. 1999. Serum concentrations of organochlorine compounds and K-ras mutations in exocrine pancreatic cancer. 354(9196):2125-2129.
266. Hoppin JA, et al. 2000. Pancreatic cancer and serum organochlorine levels. Can Epid Biomark Prev 9(2):199-205.
267. Clary T, et al. 2003. Pancreatic cancer mortality and organochlorine pesticide exposure in California, 1989-1996. Am J Ind Med 43(3):306-313.
268. Fryzek JP, et al. 1997. A case-control study of self-reported exposures to pesticides and pancreas cancer in southeastern Michigan. Int J Can 72(1):62-67.
269. Sharpe CR, et al. 2001. Activities and exposures during leisure and prostate cancer risk. Can Epid Biomark Prev 10(8):855-860.
270. Paldy A, et al. 1988. Pesticide use related to cancer incidence as studied in a rural district of Hungary. Sci Total Env 73(3):229-244.
271. Mendonca GA, et al. 1999. Organochlorines and breast cancer: a case-control study in Brazil. Int J Can 83(5):596-600.
272. Unger M, et al. 1984. Organochlorine compounds in human breast fat from deceased with and without breast cancer and in a biopsy material from newly diagnosed patients undergoing breast surgery. Env Res 34(1):24-28.
273. Van't Veer P, et al. 1997. DDT (dicophane) and postmenopausal breast cancer in Europe: case-control study. Br Med J 315(7100):81-85.
274. López-Carrillo L, et al. 2002. Serum levels of β-hexachlorocyclohexane, hexachlorobenzene and polychlorinated biphenyls and breast cancer in Mexican women. Eur J Can Prev 11(2):129-135.
275. Ward EM, et al. 2000. Serum organochlorine levels and breast cancer: a nested case-control study of Norwegian women. Can Epid Biomark Prev 9(12):1357-1367.
276. Bagga D, et al. 2000. Organochlorine pesticide content of breast adipose tissue from women with breast cancer and control subjects. JNCI 92(9):750-753.
277. Krieger N, et al. 1994. Breast cancer and serum organochlorines: a prospective study among white black and Asian women. JNCI 86(8):589-599.
278. Zheng T, et al. 2000. Risk of female breast cancer associated with serum polychlorinated biphenyls and 1,1-dichloro-2,2'-bis(p-chlorophenyl)ethylene. Can Epid Biomark Prev 9(2):167-174.
279. Zheng T, et al. 2000. Oxychlordane and trans-nonachlor in breast adipose tissue and risk of female breast cancer. J Epid Biostat 5(3):153-160.
280. Zheng T, et al. 1999. DDE and DDT in breast adipose tissue and risk of female breast cancer. Am J Epidem 150(5):453-438.
281. Zheng T, et al. 1999. Environmental exposure to hexachlorobenzene (HCB) and risk of female breast cancer in Connecticut. Can Epid Biomark Prev 8(5):407-411.
282. Zheng T, et al. 1999. Beta-benzene hexachloride in breast adipose tissue and risk of breast carcinoma. Cancer 85(10):2212-2218.
283. Hopenhayn-Rich C, et al. 2002. Regional assessment of atrazine exposure and incidence of breast and ovarian cancers in Kentucky. Arch Env Contam Toxicol 42(1):127-136.
284. Dorgan JF, et al. 1999. Serum organochlorine pesticides and PCBs and breast cancer risk: results from a prospective analysis (USA). Can Causes Contr 10(1):1-11.
285. Moysich KB, et al. 1998. Environmental organochlorine exposure and postmenopausal breast cancer risk. Can Epid Biomark Prev 7(3):181-188.
286. Wolff MS, et al. 2000. Risk of breast cancer and organochlorine exposure. Can Epidem Biomark Prev 9(3):271-277.
287. Wolff MS, et al. 2000. Organochlorine exposures and breast cancer risk in New York City women. Env Res 84(2):151-161.

288. Charles MJ, et al. 2001. Organochlorines and 8-hydroxy-2'- deoxyguanosine (8-OHdG) in cancerous and noncancerous breast tissue: do the data support the hypothesis that oxidative DNA damage caused by organochlorines affects breast cancer? Arch Env Contam Toxico 41(3):386-395.
289. Laden F, et al. 2001. 1,1-Dichloro-2,2-bis(p-chlorophenyl)ethylene and polychlorinated biphenyls and breast cancer: combined analysis of five U.S. studies. JNCI 93(10):768-776.
290. Laden F, et al. 2001. Plasma organochlorine levels and the risk of breast cancer: An extended follow-up in the Nurses' Health Study. Int J Can 91(4):568-574.
291. Helzlsouer KJ, et al. 1999. Serum concentrations of organochlorine compounds and the subsequent development of breast cancer. Can Epid Biomark Prev 8(6):525-532.
292. Hunter DJ, et al. 1997. Plasma organochlorine levels and the risk of breast cancer. N Eng J Med 337(18):1253-1258.
293. Schecter A, et al. 1997. Blood levels of DDT and breast cancer risk among women living in the north of Vietnam. Arch Env Contam Toxicol 33(4):453-456.
294. Weiderpass E, et al. 2000. Organochlorines and endometrial cancer risk. Can Epid Biomark Prev 9(5):487-493.
295. Sturgeon SR, et al. 1998. Serum concentrations of organochlorine compounds and endometrial cancer risk. Can Causes Contr 9(4):417-424.
296. Austin H, et al. 1989. A prospective follow-up study of cancer mortality in relation to serum DDT. Am J Pub Health 79:43-46.
297. Hopenhayn-Rich C, et al. 2002. Regional assessment of atrazine exposure and incidence of breast and ovarian cancers in Kentucky. Arch Env Contam Toxicol 42(1):127-136. 2002. Regional assessment of atrazine exposure and incidence of breast and ovarian cancers in Kentucky. Arch Env Contam Toxicol 42(1):127-136.
298. Wong O, et al. 1989. Ecological analyses and case-control studies of gastric cancer and leukaemia in relation to DBCP in drinking water in Fresno County, California. Br J Ind Med 46(8):521-528.

Chapter 6
Pesticides and Reproduction

There were 3.6 million babies born alive in the U.S. in 2001, and about 15,000 born dead. Estimates of spontaneous abortion, or early fetal deaths before viability, range from 50 to 65% of human conceptions. About 3% of babies have a major birth defect, which the Centers for Disease Control and Prevention (CDC) defines as "a structural or chromosomal anomaly present at birth and recognized before age six". Birth defects are the leading cause of infant mortality, accounting for about 20% of deaths. Many who desire children cannot have them because of primary infertility, estimated to affect 11% of couples in the U.S. Known risk factors, include infectious disease, advanced maternal age, tobacco, alcohol and drug use, among others, which account for less than half of adverse reproductive outcomes in humans.

Many pesticides are known to be toxic to the embryo (embryotoxic) and fetus (fetotoxic) in laboratory animals. Studies of pesticides in humans show adverse reproductive effects in males and females, and in the developing child.

Most pesticide-related reproductive disorders are not a result of acute poisoning. In one of the most severe incidents ever reported, factory workers made sterile by the soil fumigant DBCP (dibromochloropropane), had no signs or symptoms of a pesticide-related health problem during the months and years that the pesticide was destroying their ability to produce sperm. It was not until men who had fathered children noticed that they were not having the additional children they wished, that the problem was discovered.

A study in New York City found widespread pesticide use and exposure during pregnancy among a cohort of African-American and Dominican women. Pest control measures were used in the home by 85% of the women. Eight pesticides were found in 45% or more of the women . The four pesticides found in the highest concentration in personal air samples of women monitored during the third trimester were diazinon, chlorpyrifos, propoxur, and ortho-phenylphenol[1].

Birth defects (Tables 1-A, 1-B)
Studies in North America found a 166% to 249% increase in risk if the mother lived in a pesticide use area in Canada , California, or Minnesota, or if the father was a pesticide applicator. No associations with pesticide exposure were found in the malathion medfly spray program in California, or from heptachlor contaminated milk episode in Hawaii.

Studies in South America found a 210% increase for female flower workers in Colombia with the highest pesticide exposure , which decreased 40% in the low exposure group. The wives of male flower workers had a 30% increase in risk A study in Chile attributed more than half of the risk of birth defects to the mother's occupational pesticide exposure .

In Europe a 316% increase was found in Spain if the mother was an agricultural worker, but a non-significant 50% increase if it was the father. If the father handled pesticides a 49% borderline significant increase was found. The father's exposure to paraquat increased risk by 280% ; a 245% increase for glufosinate exposure was not significant. A 40% increase was found in Finland if the mother was an agricultural worker.

In Asia, a 456% increase was found in conventional Filipino farmers compared to those using IPM (Integrated Pest Management), a 429% increase in women in India who worked in pesticide sprayed cotton fields, and a non-significant increase in Chinese women exposed during pregnancy. No association with methylisocyanate exposure was found for Indian women in Bhopal[9], or in New Zealanders exposed to 2,4,5-T .

Case Reports
Pesticides associated with severe birth defects from exposure during pregnancy include 2,4-D, deet, malathion lice treatment, and metasystox-R/Phosdrin/Lannate treated crops..

Central Nervous System (excluding neural tube defects).
An increased risk of unspecified neurodevelopmental /neurobehavioral defects was reported for Minnesota applicators using glyphosate/Roundup, and the fumigant phosphine, and for hydrocephalus (spinal fluid build up in the brain) in Norway. A study in Texas found no association with maternal exposure to pesticides and Down's syndrome, which accounts for over half of all central nervous system defects.

Cleft Lip and/or Cleft Palate
The highest risk reported is a 380% increase in California for home use before and after conception . Agricultural workers were at increased risk in Finland but a 90% increase in those exposed to pesticides was not significant. An increase was found for agricultural chemical exposure in Iowa, and Michigan , in Georgia farmers, and in female farm workers in England and Wales. Living in a high pesticide use area increased risk in Arkansas and Canada . A 20% decrease was found if the father was exposed at work in England and Wales . No cases were found in 2,4,5-T applicators in New Zealand..

Cryptorchidism
Undescended testicles is one of the most common urogenital defects in males. A study in China found a 1,280% increase if the father was occupationally exposed to pesticides. A 67% increase was found in Denmark if the mother was a garden worker, but no increase if the father.

Eye Defects
Increased risk of cataracts was found if the father worked in forestry or logging in Canada, or was exposed to wood preservatives. In 1993, media reports in England alleged that clusters of anophthalmia (no eyes) and microophthalmia (eyes abnormally small), might be linked to exposure to the pesticide benomyl/Benlate®, a fungicide widely used in agriculture. Higher rates were found in rural areas of England compared to urban areas, but no association with pesticides was reported[2]. A study in Italy found a 37% decrease in risk if the parents were exposed to benomyl at work . A child born to a poisoned farm worker, had ocular hypertelorism, microopthalmia, and optic nerve colobomas among other severe defects.

Gastrointestinal Defects
Few studies report a significant association with pesticide exposure. A 232% increase was found in Norway if the parents were farmers. A 52% increase risk of tracheo-esophageal fistula was found in female farm workers in Canada; an increase in a community sprayed with malathion based on three cases was not significant.

Heart Defects
The highest risk reported is a 470% increased risk of transposition of the great arteries (TGA) if the mother exposure to rodenticides at home in the first trimester; a 280% increase found for home exposure to herbicides, and a 220% increase for any home pesticide exposure[49]. Home use increased the risk of total anomalous pulmonary venous return[51]. A California study found a 310% increased risk of cono-truncal defects for home garden pesticide use , and a 220% increase if them other used insect repellent[34]. A 203% increase was found the father worked in forestry or logging n Canada[41], and a 70% increase if the father was a licensed applicator in Minnesota[20]. Studies in Finland found no association with the mother's occupational exposure to pesticides for hypoplastic left heart syndrome[46], atrial septal defect[47], or ventricular septal defect[48].

Hypospadias
A study in Norway found a 294% increase in risk the parents were farmers[27].No association with pesticide exposure found. in male and female garden workers in Denmark[38.]

Kidney Defects
A study in Canada found a 249% increase in risk for pregnant women living in a high pesticide use area

Limb Reduction Defects
Several studies report an association of limb reduction defects with pesticide exposure. The highest risk found was a 700% increase in Australia for home use more than once in the first trimester (RR7.0), which decreased 390% if

used only once a month (RR 3.1). A 350% increased risk was found in California for periconceptual home use. A 260% increased risk was found in Washington State if the mother was a farm worker Washington State, a 231% increase in California if both parents were farm workers , and a 250% increase in Norway if the parents were farmers. In California, the risk was found to be higher if there were additional defects besides limb reduction. If the mother lived in a high pesticide use area, a 311% increase was found for multiple defects which decreased 120% if limb reduction was the only defect. If the mother lived in a high agricultural production area, a 240% increase for multiple defects decreased 70% if limb reduction was the only defect. If either parent was a farm worker a 10% decrease was found for the single defect; a 60% increase for multiple defects was not significant[53]. Of the 237 infants in the study, 67% had only limb reduction without additional defects. In the 23% with additional defects, a trend of increasing risk with increasing exposure to agricultural production was found[53].

Neural Tube Defects

Spina bifida and anencephaly result when the neural tube, which develops into the brain and nervous system, fails to close properly in the first 28 days after conception. There has been a world-wide decrease in the incidence of neural tube defects with the recognition of the importance of folic acid for normal neural tube development, and the implementation of food enrichment and vitamin supplementation programs. The studies described did not account for possible effects of folic acid. For example, the highest reported risk is a 780% increase in China if the mother was exposed to pesticides in the first trimester. Recent studies in China report a dramatic decrease in neural tube defects associated with folic acid supplementation.

If the mother was a farm worker, increased risk was found in The Netherlands (OR 5.6, OR 3.4), Finland (OR 1.9), Texas, and England; and for Swedish women living on a farm , and in Norway if the parents were farmers (OR 2.76). An increase in farm worker women in Spain was not significant, nor were increases if the father was a farm worker in The Netherlands. Non-significant increases were found if the father was exposed at work in England and Wales, with a 20% decrease in risk of spina bifida (RR 0.8), but no association with anencephaly. A 9% decrease in risk was found in Texas for gardeners and landscapers (OR 0.91).

A California study found a 290% increased risk if the mother applied pesticides in the home , which was borderline significant if the home was commercially treated. Living two and a half miles or less from a crop production area in California increased risk by 150% . An increase was found in mothers living in a high forestry/agricultural use area in Canada. A study of a cluster of neural tube defects in a suburban area of Northern California found no association with pesticide exposure.

When a high rate of neural tube defects was found in Matamoros, Mexico, across the border from Brownsville, Texas, pesticides were suspected. A study of Mexican-American women on the Texas/Mexico border found no association with the parents' exposure to pesticides.

Urogenital Defects

The most common urogenital defects are hypospadias and cryptorchidism in males. Defects in this category also include ambiguous genitalia among others. Two studies reported an increase in urogenital defects without specifying the type– a 170% increase if the father was a licensed pesticide applicator, and an increase if the father was exposed to wood preservatives and chlorophenols.

Spontaneous Abortion (Table 2)

Spontaneous abortion (miscarriage) is fetal loss in the first 20 weeks of pregnancy. The highest reported risk is a 760% increase in wives of pesticide applicators in Italy. Increased risk was found in farm wives in Minnesota and Canada , in wives of cotton field workers in India, and a 583% increase in Indian couples working in pesticide treated vineyards. A 617% increased risk was found in Filipino farmers using conventional methods compared to those using the less pesticide intensive IPM (Integrated Pest Management).

Chinese women exposed during pregnancy had a 390% increased risk of threatened abortion, and for spontaneous abortion if worked during pregnancy. A 240% increased risk was found in Canadian agricultural / horticultural workers, 220% in Colombia flower workers, 80% in Minnesota female pesticide applicators, and increased risk in Spanish greenhouse sprayers. A 90% increased risk was found in Norwegian farmers, which increased to 240% in

grain farmers with a poor yield. The authors postulate that a later harvest results in higher levels of mycotoxins which may increase risk.

Exposure of the father to pesticides can increase the risk of spontaneous abortion. A 300% increase was found in DBCP (dibromochloropropane) exposed banana workers in Israel, and in Canadian farmers. A case report from Canada found a non-significant 500% increased risk in a farm couple when the husband applied 2,4-D without using protective clothing or equipment, which decreased 250% when he used protection.

Increased risk was found in survivors of the 1984 toxic release in Bhopal, India compared to unexposed controls (PR 4.29), and in women who were pregnant at the time of the accident. Women poisoned by hexachlorobenzene in Turkey in the 1950s had a lifetime increase in risk compared to the unexposed.

Ethylene oxide (ETO) is a gas used to sterilize hospital and dental equipment. An increased prevalence of spontaneous abortion was found in Finnish hospital workers exposed during pregnancy, and a borderline significant increased risk found in California dental assistants.

Several studies found no association between pesticides and spontaneous abortion including female farm workers in Bulgaria, workers exposed to chlorinated hydrocarbon insecticides in Germany, and Italy, in a California community sprayed with malathion for medfly control, with DDE and DDT serum levels in Florida women, in crop duster pilots compared to their siblings, and in a 17 year follow-up of DBCP workers in Israel. A 10% decrease in risk was found in female greenhouse workers in Denmark (OR 0.90), and an 11% decrease in the wives of herbicide sprayers in New Zealand (RR 0.89).

Stillbirth (Table 3)
Unlike early fetal loss, which may go unrecognized and unreported, deaths of infants prior to delivery are documented and recorded. An 840% increase in Hispanics living near a pesticide factory in Texas is the highest reported. A 553% increase was found in female agricultural workers in Canada, and lower increases in California (OR 1.6), and Washington State (OR 1.5). A 329% increase was found in wives of pesticide exposed cotton field workers in India. A California study found a 240% increased risk from occupational exposure to unspecified pesticides, a 170% increase from home use, both borderline significant, and Canadian women studies. A U.S. national study of self-reported use found a 50% increase in risk if the mother used pesticides at home, a 30% increase if the father, and a 20% borderline significant increase in risk if the father was exposed at work. U.S. Navy personnel were at increased risk if either parent was exposed.

Living in a high pesticide use area in Canada increased risk 250%. A 30% increase in women living in pesticide use areas in California was borderline significant. No increase was found for community malathion spraying, in wives of Minnesota pesticide applicators, or in women in Bhopal, India who were pregnant at the time of the accident. In Colombia flower workers an 11% decreased risk was found in wives of male worker and a 1% decrease in female workers.

Fertility (Table 4)
Past Incidents:
Two pesticides are known to cause sterility in humans, both in male factory workers. The first episode occurred in a single facility, affecting about 100 severely poisoned workers and was soon recognized. Primary effects were on the nervous system, but testicular dysfunction was also found. In the second episode there were no warning signs of acute poisoning, allowing exposure to continue for months and years before recognition of the problem. Testicular failure was the primary effect with no other apparent disorders. Both pesticides, now banned in the U.S., are still being monitored as environmental contaminants of surface and ground water in California and Virginia.

The first pesticide is kepone (chlordecone), a persistent chlorinated hydrocarbon insecticide produced at a substandard facility in Hopewell, Virginia, a small town on the James River. The plant was opened in 1974 and closed by the Commonwealth of Virginia in 1976.

The second pesticide is DBCP (dibromochloropropane), a soil fumigant that was widely used in agriculture as a

nematicide. The first reports of sterility were from an Occidental Chemical Company plant in Lathrop, California. Further investigations found testicular dysfunction in men exposed to DBCP in Dow and Shell Chemical Company workers in Colorado, Alabama, Arkansas, and Michigan, and other workers in the U.S. and throughout the world. Many more workers were affected by DBCP because of its high production volume, widespread use, and the long silent period of damage to the testes until exposure ceased.

Recent Developments:
Because no recent incidents comparable to kepone and DBCP have occurred does not mean that other environmental and workplace exposures are not affecting human fertility. The major known risk known factor for infertility in otherwise healthy people is infections from sexually transmitted diseases; alcohol, tobacco, and drug use also contribute. Studies of infertility in human often compare medically diagnosed infertile couples with fertile couples. Such studies are useful but have shortcomings when determining the role of environmental contaminants and occupational exposures in healthy people. The infertile couples are not representative of the general population; the controls are usually drawn from hospital based clinics. It is necessary to determine which partner is infertile and analyze the data based on male or female factor infertility. The studies require a large number of cases and controls, who are often difficult to recruit and follow over time.

A more recent development is an easily collected measure of fertility that includes both partners, and can be done in any randomly selected population. It is called 'time to pregnancy', or fecundability. Fecundability is the number of months or menstrual periods it takes to conceive a child when not using birth control. The resulting fecundability ratio is a measure of the fertility rate in exposed couples compared to non-exposed couples. A ratio of one means there is no difference in fertility between them. A ratio greater than one means the exposed couples get pregnant in a shorter period of time, that they are 'more fertile'. A ratio less than one means the exposed couple takes longer to get pregnant, that they are 'less fertile'. The lower the ratio the less fertile (fecund) the couple.

Fecundity:
Several studies report decreased fecundity in pesticide exposed workers. In the Netherlands, pesticide exposed fruit growers had an 18% lower fertility rate (FR 0.82), with an additional 40% decrease in spray season (FR 0.42) . A 22% decrease in the fertility rate was found in female greenhouse workers in Denmark who sprayed pesticides (FR 0.78), with an additional 11% decrease if they did not use gloves (FR 0.67). A 17% decrease in the fertility rate was found in pesticide exposed greenhouse workers in Denmark and France (FR 0.83)[106]. In Canada the amount of time females spent in farm pesticide activity decreased the fertility rate 20 to 49% across several use categories. No association was found with sterility. Male greenhouse sprayers in Italy had a 240% increased risk of a 3 months or more delay in conception, compared to other greenhouse workers who had a 60% increase that was not significant. Another study of pesticide exposed Italian greenhouse workers found a 5.4 month delay in conception compared to 3.9 months for unexposed workers.

Increased fecundability ratios have also been found in pesticide exposed workers. Danish farmers who had used pesticides for 11 to 15 years had a 61% increased fertility rate (FR 1.61, and a 30% increase if exposed 6 to 10 years, (FR 1.30 borderline significant). Pesticide exposed farmers in Denmark and France had 9% increased rate (FR 1.09), and vineyard workers in France a 17% increase.

No significant difference in fecunability was found between traditional and organic farmers.

Infertility:
Several studies comparing fertile couples to medically diagnosed infertile couples have considered pesticides as a risk factor for infertility. In Austria that working in agriculture greatly increased the risk of male infertility. Iowa women who ever worked in agriculture had a 700% increased risk of infertility which was 430% higher if prior to diagnosis; living on a farm increased risk 80%. In California no association with infertility was found in male factory workers exposed to carbaryl, or field applicators of DBCP.

Table 1-A
Birth Defects and Pesticide Exposure - Increased Risk
(See Appendix F for explanation of the table)

Any Major Defect(s)	
Canada NB living in high pesticide use area[(a)2]	SRR 2.49
Chile mother exposed pesticides at work[3]	AR[(b)] 54%
China pesticides at work during pregnancy[4]	OR 1.8 ns[#]
Colómbia female flower workers high exposure[5]	RR 2.1
Female flower workers low exposure	RR 0.6
Wives male workers employed 1-15 yr[6]	OR 1.3
Finland mother an agricultural worker[7]	OR 1.4 [*]
Hungary cluster trichlorfon in fish farming[©)8]	11/15 births
India exposed cotton field workers female[(d)9]	OR 4.29
India Bhopal MIC[(e)] exposure[10]	No assoc.
New Zealand live 2,4,5-T application area[11]	IR > 1[#]
New Zealand 2,4,5-T sprayers[12]	RR 1.19[#]
Norway agricultural workers[13]	No assoc.
Philippines conventional farming vs IPM[(f)14]	RR 4.56
Spain mother an agricultural worker[15(g)]	OR 3.16
Father an agricultural worker	OR 1.5[#]
Father a pesticide handler	OR 1.49[*]
Spain father exposed to paraquat[16]	OR 2.80
Father exposed to glufosinate	OR 2.45[#]
US California mother lives pesticide use area[(h)17]	OR 1.4[#]
Halogenated hydrocarbon pesticide use	OR 2.2
US California malathion medfly spraying[18]	No assoc.
US California placental p,p'-DDE levels[19]	No assoc.
US Hawaii heptachlor milk contamination[(I)20]	No assoc.
US Minnesota licensed applicators[21]	OR 1.96
General population wheat crop area	OR 1.86
Living in high pesticide use area	OR 1.66
Case Reports	
England 2,4-D leaky sprayer multiple defects [(j)22]	-
France mother exposed urogenital defect[23]	-
Germany deet use multiple severe defects[(k)24]	-
Netherlands malathion for lice 1st trimester[25]	-
US California farm worker reentry poisoning[(l)26]	-
Central Nervous System	
Finland agriculture/horticulture 1st trimester[27]	OR 1.0
Norway farmer parents hydrocephalus[28]	OR 3.49
US Colorado father agriculture/forestry[(m)29]	OR 2.3 [*]
US Minnesota glyphosate herbicide users[(n)30]	OR 3.60
Phosphine applicators	OR 2.48
US Texas maternal exposure[(o)] Down syndrome[31]	No assoc.
Cleft Lip/Palate	
Canada NB living in high pesticide use area[(a)1]	SRR 2.49
England/Wales gardener/farm worker females[32]	Increase
England/Wales father exposed[33]	RR 0.8
Finland mother agricultural worker[6]	OR 1.9
Pesticide exposed vs unexposed	OR 1.9[#]
Finland agriculture/horticulture 1st trimester[26]	OR 3.3
New Zealand 2,4,5-T sprayers[11]	Not found
US Arkansas live 2,4,5-T application area[34]	Increase
US California periconceptual home use[35]	OR 3.8
Father occupational exposure	OR 1.7 [*]
US Georgia farmers periconceptual exposure[36]	OR 3.3 [*]
US Iowa agricultural chemical use[37]	OR 2.85
Michigan agriculture chemical use	OR 1.68
Cryptorchidism[(p)]	
China father occupational exposure[38]	OR 12.8
Denmark female garden workers[39]	OR 1.67
Male garden workers	No assoc.
US CPP[(q)] maternal DDE levels[40]	OR 1.3[#]
Eye Defects	
Canada father exposed WPs[®)], chlorophenols[41]	Increase
Canada father's occupation forestry/logging[42]	OR 2.28
England severe cases eye defects[(s)43]	OR 2.4
All cases	OR 1.8
Italy parental occupational exposure benomyl[44]	OR 0.63
Gastrointestinal Defects	
Canada agriculture/horticulture females TEF[(t)45]	OR 1.52
Norway farmer parents[27]	OR 2.32
US California malathion spraying TEF[(t)46]	RR 2.66[(u)#]
US CPP[(q)] maternal DDE levels[39]	OR 1.9 [*]
(Continued in Table 1-B)	

* borderline significance
\# not statistically significant

(a) Fenitrothion, aminocarb, phenoxy/other herbicides. **(b)** Attributable Risk is the percentage accounted for by pesticide exposure. **[c]** Cluster ceased when trichlorfon banned. **(d)** 80% had symptoms of moderate poisoning. **(e)** Methylisocyanate, toxic gas released from an explosion in Dec. 1984 at a factory manufacturing carbaryl (Sevin). **(f)** Integrated Pest Management. **(g)** During the month before conception and first trimester. **(h)** During weeks 3-8 pregnancy in the sq. mile of residence area. **(I)** From 1980-1982 pineapple waste contaminated with heptachlor was used in feed for dairy cows. **(j)** Both parents applied 6 days/week, 7 hoursr/day before conception to 5 weeks after last menstrual period; mother had severe burn from spill on leg. **(k)** Applied daily entire pregnancy (also took chloroquine). **(l)** From exposure to metasystox-R, Phosdrin, and /Lannate on cauliflower first month of pregnancy. Child died with severe multiple defects. **(m)** In craniosynostosis the sutures of the skull fuse prematurely resulting in an abnormally shaped head. **(n)** Neurodevelopmental and neurobehavioral defects. **(o)** 3 months before to after last menstrual period. **(p)** Undescended testicles. **(q)** Collaborative Perinatal Project, a cohort 1959-1965 study of pregnant women and their children at 12 medical centers (about 56,000 pregnancies). **[r]** Wood preservatives. **(s)** Anophthalmia/microophthalmia, alleged clusters linked to the fungicide benomyl. ORs are for rural vs urban areas. **(t)** Tracheo-esophageal fistula. **(u)** Based on three cases.

Table 1-B
Birth Defects and Pesticide Exposure
(See Appendix F for explanation of the table)

Heart Defects	
Canada father's occupation forestry/logging[41]	OR 2.03
Finland mother work exposure HLHS[(a)47]	No assoc.
Finland mother work exposure ASD[(b)48]	No assoc.
Finland mother work exposure VSD[©)49]	No assoc.
Finland agriculture/horticulture 1st trimester[26]	OR 0.3
New Zealand live in 2,4,5-T application area[10]	IR > 1#
US California periconceptual home use CT[(d)34]	OR 3.1
Maternal use insect repellent CT[(d)]	OR 2.2
US Maryland BWIS[(e)] any home use 1st trim.[50]	OR 2.0
Mother home rodenticide exposure	OR 4.7
Mother home herbicide exposure	OR 2.8
Mother home insecticide exposure	OR 1.5 *
Any home pesticide exposure[51]	AR[(f)] 5.5%
US Maryland BWIS[(e)] TAPVR[(g)] pesticides[52]	OR 2.74
US Minnesota licensed applicators[20]	OR 1.7
Hypospadias[(h)]	
Denmark male and female garden workers[38]	No assoc.
New Zealand live 2,4,5-T application area[10]	IR > 1#
Norway farmer parents[27]	OR 2.94
Kidney Defects	
Canada NB living in a high pesticide use area[(a)1]	SRR 2.49
Limb Reduction Defects	
Australia home use more than once 1st trim.[53]	RR 7.0
Home use once during 1st trimester	RR 3.1
Norway farmer parents[27]	OR 2.50
US California periconceptual home use[34]	OR 3.5
US California mother high pesticide use area[(l)54]	RR 3.1
Mother lives high pesticide use area[(j)]	RR 1.9
Mother high agricultural production area[(l)]	RR 2.4
Mother high agricultural production area[(j)]	RR 1.7
Either parent an agriculture worker[(l)]	RR 1.6#
Either parent an agricultural worker[(j)]	RR 0.9
US California one/both parents farm workers[55]	RR 2.31
US National crop dusters vs siblings[56]	No assoc.
US New York State parent pesticide exposed[57]	OR 0.9
Farming occupation	OR 1.1#
US Washington State mother exposed at work[58]	PR 2.6
Musculoskeletal Defects	
Finland mother works in agriculture[6]	OR 1.9
US Minnesota licensed applicators[20]	OR 1.5

Neural Tube Defects[(k)]	
Canada father exposed WPs[(l)40], chlorophenols	Increase
Canada NB living in a high pesticide use area[(m)1]	SRR 2.49
China mother exposed 1st trimester[59,60]	OR 7.8
England/Wales gardeners/agriculture females[31]	Increase
England/Wales father exposed[32]	RR 1.2#
Spina bifida	RR 0.8
Farmers (anencephaly)	RR 1.0
Gardeners	RR 2.3#
Finland mother works in agriculture[6]	OR 1.9
Finland agriculture/horticulture 1st trimester[26]	OR 1.0
Hungary maternal work in agriculture[61]	OR 1.1#
Netherlands mother works in agriculture[62]	OR 5.6
Netherlands agricultural job females[63]	OR 3.4
Netherlands father exposed[64]	OR 1.7#
Norway farmer parents[27]	OR 2.76
Spain mother agricultural worker[(n)14]	OR 2.2#
Sweden women living on a farm[65]	OR 2.2
US California home use mother applied[34]	OR 2.9
Commercial home application	OR 2.5 *
Mother lives within 2.5 miles crop area	OR 1.5
US California Antioch cluster investigation[66]	No asso.
US Texas father farm /ranch work[67]	$\chi^2$1.8 p<.001
Mother farm/ranch work	$\chi^2$1.3 p<.05
Parental pesticide exposure occupation	OR 1.28#
Hired farm workers/ranch workers	OR 1.73#
Gardeners and landscapers	OR 0.91
US/Mexico parental exposure pesticides[68]	Noassoc.
Urogenital Defects[(o)]	
Canada father exposed WPs[(l)40], chlorophenols	Increase
New Zealand 2,4,5-T sprayers[11]	Not found
US CPP[(p)] maternal DDE levels[39]	OR 1.2#
US Minnesota licensed applicators[13]	OR 1.7

* borderline significance
\# not statistically significant

(a) Hypoplastic left heart syndrome. **(b)** Atrial septal defect (secundum). **[c]** Ventricular septal defect. **(d)** Cono-truncal defects. **(e)** Baltimore-Washington Infant Study, a population-based case- control study of cardiovascular defects. **(f)** Attributable Risk, the percentage accounted for by pesticide exposure. **(g)** Total anomalous pulmonary venous return. **(h)** The opening of the urethra (where urine comes out) is not at the tip of the penis but on the underside. **(l)** Had other defects in addition to limb reduction. **(j)** Limb reduction the only defect. **(k)** Neural tube defects (spina bifida, anencephaly). **(l)** Wood preservatives. **(m)** Focus on fenitrothion, aminocarb, phenoxy/other herbicides. **(n)** During the month before conception and the first trimester. **(o)** Not specified. Cryptochidism and hypospadias most common. **(p)** Collaborative Perinatal Project, a 1959-1965 cohort study of pregnant women and their children at 12 medical centers (about 56,000 pregnancies).

Table 2
Spontaneous Abortion and Pesticide Exposure
(See Appendix F for explanation of the table)

Bulgaria farm workers female[69]	No assoc.	Israel DBCP wives exposed banana workers[(m)81]	PR 3.0
Canada Ontario late[(a)] thiocarbamate use[70]	OR 1.8	Only wives conceived before & after expos.	PR 4.66
Late[(a)] glyphosate use[(c)]	OR 1.7	Italy wives pesticide applicators[82]	OR 7.6
Early[(b)] phenoxy herbicide use[(c)]	OR 1.5	Spontaneous abortion/pregnancy ratio[(l)]	OR 3.8
Early[(b)] any herbicide use[(c)]	OR 1.4	Italy hexachlorobenzene, DDT compounds[83]	No assoc.
Early[(b)]triazine herbicide use[(c)]	OR 1.4*	New Zealand wives herbicide sprayers[49]	RR 0.89
Canada preconceptual use 2,4-D by husband[71]	OR 2.5*	Norway late[(n)] farmer parents[84]	OR 1.9
Using 2,4-D without protective equipment	OR 5.0#	Parents grain farmers	OR 1.8
Canada Ontario farm pesticide use males[(d)72]	Increase	Poor grain harvest[(o)]	OR 2.4
Canada Quebec agric/horticulture females[(e)73]	OR 2.4	Philippines conventional farming vs IPM[(p)9]	RR 6.17
China mother pesticide work pregnancy[(f)3]	Increase	Spain female greenhouse sprayers[85]	Increase
China mother work exposure (threatened)[42]	OR 3.9	Turkey HCB[(q)] females 40 years later[86]	Increase
Colómbia female flower workers[5]	RR 2.20	US California malathion medfly spray[45]	No assoc.
Wives of male workers[(g)]	RR 1.79	US California ETO[(h)] dental assistants[87]	OR 2.5*
Denmark greenhouse female pesticide users[(i)74]	OR 2.0#	US Florida DDT, DDE blood levels[88]	No assoc.
Outdoor garden workers	OR 1.3#	US Minnesota wives Cheyenne[(r)] users[89]	RR 2.9
Female greenhouse workers female	OR 0.9	Wives imidizolinone users	RR 2.6
Finland ETO[(h)] hospital workers[75]	PR 1.1	Wives sulfonylurea users	RR 2.1
Exposure during pregnancy	PR 2.98	Female pesticide appliers	RR 1.8
Germany CH[(j)] repeated exposure[76]	No assoc	Wives fungicide appliers	RR 1.6
India Bhopal MIC[(k)] vs unexposed[9]	PR 4.29	Wives herbicide appliers 1st trimester[(s)]	Increase
India Bhopal MIC[(k)] pregnant during accident[77]	Increase	US National crop dusters vs siblings[55]	No assoc.
India wives exposed cotton workers[8]	OR 1.74		
India couples exposed in vineyards[78]	PR 5.83		
Israel DBCP production 17 year follow-up[79]	No assoc	* borderline significance	
Israel DBCP production workers[80]	No assoc	# not statistically significant	

(a) 12-19 weeks gestation. (b) 12 weeks gestation. **[c]** 3 months before to month of conception. **(d)** Thiocarbamates, carbaryl, other pesticides. **(e)** Fetal death after 27 weeks, employed > 30 hrs/wk for > 2 wks any time during pregnancy. **(f)** Risk increased with increasing number pesticides used. **(g)** Employed at least 6 months for one of 58 floriculture companies. **(h)** Ethylene oxide, a gas used to sterilize equipment. **(I)** Union members. Only 9% authorized to spray pesticides. **(j)** Chlorinated hydrocarbon pesticides: pentachlorophenol, lindane, hexachlorobenzene, DDT group. **(k)** Methyliso-cyanate, toxic gas released December 1984 after explosion at factory making carbaryl (Sevin). **(l)** 0.27 in appliers versus 0.07 in controls. **(m)** Whose wives conceived before and after DBCP exposure. **(n)** 16-27 weeks gestation. **(o)** Later harvest results in higher exposure to mycotoxins. **(p)** IPM = Integrated Pest Management. **(q)** Hexachlorobenzene. 1950s outbreak of porphyria cutanea tarda from eating treated seed wheat not meant for consumption. **[r]** Thifensulfuron/tribenuron, fenoxaprop-P-ethyl/MCPA. **(s)** During the time when herbicides are applied.

Table 3
Stillbirth and Pesticide Exposure
(See Appendix F for explanation of the table)

Canada Quebec low-level exposure females[(a)90]	OR 3.1
Canada Quebec pesticides/germicides females[91]	OR 2.06
Canada Quebec agric/horticulture females[(b)72]	OR 5.53
Canada NB living in high pesticide use area[1]	SRR 2.5
Colómbia flower workers female[5]	RR 0.99
Wives of male workers[(c)]	RR 0.89
Colómbia female flower workers[4]	OR 0.99[#]
Wives of male workers	OR 0.89[#]
India Bhopal MIC[(d)] survivors vs unexposed[9]	OR 2.49
Perinatal/neonatal mortality	OR 1.37
India Bhopal MIC[(d)] pregnant during incident[76]	No assoc.
India wives of exposed cotton field workers[8]	OR 3.29
Sudan farmers hospital group females[92]	AR[(e)]34.5%
Farmers community group female	AR[(e)]22.6%
Not farmers community group females	AR[(e)]15.7%
Turkey 40 years after HCB[(f)] incident females[85]	No assoc.
US California mother lives carbamate use area[(f)93]	OR 1.3[*]
Lives halogenated hydrocarbon use area[(g)]	OR 1.3[*]
Lives estrogenic pesticide use area[(g)]	OR 1.4[#]
US California pesticide exposure at work[94]	RR 2.4[*]
Home pesticide use	RR 1.7[*]
US California placental DDE levels[18]	No assoc.
US California malathion medfly spraying[45]	No assoc.
US Massachusetts Boston chlorinated water[95]	OR 2.6[*]
U Minnesota wives of pesticide applicators[20]	No assoc.
US National mother home pesticide use[96]	OR 1.5
Mother pesticide exposure at work	OR 1.6
Father home pesticide use	OR 1.3
Father pesticide exposure at work	OR 1.2[*]
US Navy pre-term birth either parent exposed[97]	Increase
US Texas near pesticide factory Hispanics[(h)98]	OR 8.4
US Washington state farm workers[99]	OR 1.5

* borderline significance
\# not statistically significant

(a) After 28 weeks gestation. **(b)** Fetal death after 27 weeks, employed > 30 hrs/wk > 2 wks any time during pregnancy.**[c]** Worked at least 6 months for one of 58 floriculture companies. **(d)** Methyisocyanate, toxic gas released in December 1984 after an explosion at a factory making carbaryl (Sevin) **(e)** Attributable Risk, percentage accounted for by pesticide exposure. **(f)** Hexachlorobenzene. 1950s outbreak of porphyria cutanea tarda from eating treated seed wheat not meant for consumption. **(g)** During weeks 3-8 of pregnancy within a square mile of residence, or in one of adjacent 8 sq mi. areas. **(h)** Making arsenicals. High exposure group >100 ng/m^3

Table 4
Fertility and Pesticide Exposure
(See Appendix F for explanation of the table)

Austria male infertility work in agriculture[100]	OR 11.34
Canada DDE IVF[(b)] fertilization failure[101]	Increase
Canada CHI[(c)] rate/time to cleavage 1st egg[102]	No assoc.
Canada 6/13 pesticide exposure farm females[103]	FR[(d)]0.51-0.8
Farm pesticide use males only	FR 0.75-1.50
Sterility	No assoc.
Canada occupational chlorophenol exposure[104]	No assoc.
Canada pesticides female infertility[(e)105]	OR 3.02
Denmark female greenhouse pesticide sprayers[106]	FR[(d)] 0.78
Not using gloves	FR 0.67
Handling cultivars many hours/week	FR 0.69
Denmark tradition pesticide use 11-15 yrs[107]	FR[(d)] 1.61
Tradition pesticide use 6-10 yrs	FR 1.30[*]
Traditional vs organic farmer	FR 1.03[#]
Pesticide user vs non-user	FR 1.18[#]
Denmark/France pesticide exposed farmers[108]	FR[(d)] 1.09
Greenhouse workers	FR 0.83
England pesticide spray crew[(f)] impotence[109]	80% (4/5)
Recovery time in months	3-13 months
France vineyard workers fertility[98]	FR[(d)] 1.17
France infertile farm couple lindane use[(g)110]	Case report
Italy delayed conception[(h)] male sprayers[111]	OR 2.4
Greenhouse workers males	OR 1.6[#]
Italy greenhouse mean time to pregnancy[112]	5.4 months
Unexposed controls	3.9 months
Netherlands pesticides fertilization rate[113]	OR 0.38
Moderate pesticide exposure	OR 0.52 ns [#]
Heavy pesticide exposure	OR 0.22
Netherlands fruit growers spray season[114]	FR[(d)] 0.42
Fruit growers before spray season	FR 0.82
US California carbaryl fathering children[115]	No assoc.
US California DBCP applicators infertility[116]	Not found
US Iowa females agriculture work infertility[(i)117]	OR 7.0
Females agriculture work prior to infertility	OR 11.3
Residing on a farm	OR 1.8

* borderline significance
\# not statistically significant

(a) Fertility, the ability to conceive a child. **(b**) In vitro fertilization. Levels in serum, follicular fluid. **[c]** Chlorinated hydrocarbon insecticides: chlordane, DDE, heptachlor epoxide, HCB, oxychlordane **(d**) Fecundability Ratio: the likelihood of pregnancy for exposed couples vs unexposed control couples. A ratio less than 1 means a decrease in the fertility rate. The higher the ratio the more fertile (fecund) the couple. Also called 'time to pregnancy', it is the number of menstrual cycles/months to conceive when not using birth control. **(e**) Infertility: inability to conceive after 1 year of unprotected intercourse; failure to deliver a live-born child. **(f)** Using 5 organophosphates, dinoseb, paraquat, dieldrin, 3 phenoxy herbicides, simazine, linuron, mancozeb. **(g**) Successful pregnancy after protective measures taken. **(h**) 3 months or more. **(i)** All male partners diagnosed as fertile.

In vitro Fertilization (IVF):
In the Netherlands, a 62% decrease in rate of IVF (OR 0.38) was found if the couple was exposed to pesticides. The rate decreased 16% further if heavily exposed. In Canada, an increased failure rate of IVF was associated with levels of of DDE in serum and ovarian follicular fluid[100]. Another Canadian study found no association between chlorinated hydrocarbon pesticides in ovarian follicular fluid and rate or time to cleavage of the first egg.

Sperm Parameters (Table 5)
Men with sperm counts lower than 20 million sperm per milliliter of semen (m/ml) have a condition called oligospermia. Some oligospermic men conceive children. Men with a sperm count of zero have a condition called azoospermia, and cannot father children. The major cause of azoospermia is vascetomy The following discussion describes pesticide related sperm parameters in men without vasectomies.

Sperm Counts:
Many studies have been done of DBCP exposed workers since the first report in 1977 of sterility in the Occidental workers in California. DBCP is a prototype against which other suspected reproductive toxins are measured, since the studies show a strong dose response–the greater the amount and duration of exposure the more severe the damage to the testes, and the effect on sperm production.

Sperm Count
Low Normal - 20-39 million
Oligospermia - 20 million or less
Azoozpermia - no sperm

Sperm Characteristics
Motility
Necrospermia (dead sperm)
Teratospermia (abnormal shapes)

Another study was done at the Occidental plant of 154 DBCP exposed workers, and 52 exposed to other pesticides manufactured there (diazinon, dinoseb, endosulfan, malathion, maneb, methyl parathion, parathion, toxaphene, and zineb). The median sperm count in DBCP exposed was 46 m/ml versus 79 m/ml in unexposed. Azoospermia was found in 13% of exposed versus 2.9% of unexposed.; oligospermia in 6.8% of exposed and none of the unexposed. Low normal counts (20-30 m/ml)were found in 15.8% of exposed versus 5.7% of unexposed workers. A summary of findings in fourteen U.S. studies found a mean sperm count of 107.1 m/ml, a median of 83.0 m/ml;, and sperm counts less than 20 m/ml in 8.7%.

An international study found azoospermia in 64% of DBCP applicators exposed three years or more. In the Phillippines, oligospermia or azoospermia was found in 90% of exposed workers. A follow-up of DBCB workers in Israel found recovery in 30% of azoospermics and 50% of oligospermics over a period of three to four years.

Ethylene dibromide (EDB), a fumigant similar to DBCP also causes sterility. EDB exposed papaya workers in Hawaii had a mean of 80.99 m/ejaculate compared to 139.8 m/ml in unexposed controls.

In Denmark, a report that a self-selected group of organic farmers attending a convention had higher sperm counts than traditional farmers created quite a stir. Press coverage was extensive, assuming that pesticides used by traditional farmers were harming the testes. A well designed study using a random sample of a larger number of farmers did not support the earlier findings. The mean sperm count of 64 m/ml found in organic farmers was 10% higher than the 58 m/ml in traditional farmers, but the difference was not significant. A study of pesticide exposure in Danish farmers found 197 m/ml before pesticide exposure, decreasing 22% to 152 m/ml after exposure, but the difference was not significant. Decreased counts were found in farmers in Argentina using 2,4-D or for any farm pesticide exposure.

Biomarkers of Testicular Dysfunction

Increased
LH: Leutenizing hormone
FSH: Follicle stimulating hormone
SHBG: Sex Hormone Binding Globulin

Decreased
Testosterone
Inhibin B

Sperm Characteristics: **Motility**
In Argentina, a 50% decrease in sperm motility was found in farmers using 2,4-D, and a 95% decrease in an infertile French farm couple using lindane without protection, which improved to a 20% decrease with protection.

Necrospermia:
A 225% increase in necrospermia (dead sperm) was found in Argentinian farmers using 2,4-D. An infertile French farm couple in which the husband used lindane without protection had a 60% prevalence of necrotic sperm which resolved completely once protections were used. No changes were found in ethylene dibromide exposed workers in Hawaii

Teratospermia:
A 216% increase in teratospermia (abnormal shapes) was found in Argentinian farmers using 2,4-D, and a 69% increase in ethylene dibromide exposed workers in Hawaii. Danish farmers with heavy pesticide exposure had a 60% decrease in normal sperm; those with low exposure a 14% decrease. Farmers exposed ten years or more had a 40% decrease compared to farmers exposed for five years. A 60% prevalence in an infertile French farm couple using lindane without protection, persisted even after protective measures were taken.

Aneuploidy:
Chinese pesticide factory workers had a 36% higher number of sperm with abnormal number of chromosomes than unexposed workers. No associations were found with fungicide exposure in Finnish farmers.

Hormone Levels
Hormone which increase or decrease with testicular dysfunction are useful biomarkers of male infertility and sterility. Hormones that increase with testicular dysfunction are LH (leutenizing homone), and FSH (follicle stimulating hormone). Testosterone decreases with testicular dysfunction. Sex hormone binding globulin(SHBG) is a serum protein that binds testosterone. Biologically active testosterone is free and unbound. A high SHBG means less free testosterone so the higher the SHBG level, the lower the testosterone level. Inhibin B is a glycoprotein secreted by Sertoli cells in the testes that correlates with sperm count. The higher the sperm count, the higher the inhibin B level.

High LH and FSH levels were found in Chinese pesticide factory workers, in German workers with short term exposure to pesticides, in Israeli DBCP workers 17 years after exposure ceased, and in lindane factory workers. No increase was found in Minnesota herbicide applicators, vinclozolin factory workers, and molinate factory workers.

Decreased levels of testosterone were found in Chinese pesticide factory workers, Danish farmers, lindane factory workers, and black farmers in North Carolina exposed to DDT. No significant association with pesticide exposure was found in Minnesota herbicide applicators, vinclozolin factory workers, or molinate factory workers. High inhibin B levels and a high testosterone/SHBG ratio was found in Danish organic farmers.

Sex Ratio (Table 6)
More boys are conceived than girls, but more boys die, resulting in a roughly equal sex ratio in surviving infants. A shift in the sex ratio where more females are conceived can be an indicator of adverse reproductive effects. The most striking evidence of a pesticide effect on the sex ratio was found in Israel among the children born to men exposed to DBCP. Long term follow-up studies found the proportion of males conceived prior to exposure was 52.9%, during exposure 35.2%, and after recovery from testicular failure, 16.6%.

Excess female births were found in Minnesota pesticide applicators, especially fungicide users; but male infants predominated in those with birth defects. Excess female births were found in a high level compared to a low level boron village in Turkey, and in California borate workers, but the differences were not significant. In Turkey, women exposed to hexachlorobenzene at the peak of the episode from 1955 to 1957, had a lower lifetime proportion of males than those exposed at a later date. The women's lifetime spontaneous abortion rate predicted the percent males per subject. No effect of pesticides on the sex ratio was found in a national study in Canada, in DBCP water contamination areas in California, and in a national cohort of molinate factory workers.

Reproductive Fluids and Tissues
Two recent developments are dramatically changing the assessment of risks to human reproduction from environmental contaminants. The first is the increasing ability to detect extremely low levels of chemical contaminants in biological samples. The second is a rethinking of the most basic concepts in toxicology–"the dose

makes the poison"[a] when the exposure is to the developing fetus. The dose- response model dominates risk assessment, and is the basis of setting thresholds, or allowable levels of exposure to toxic chemicals. A recent review suggests that the hormetic model, characterized by low-dose stimulation and high-dose inhibition is more prevalent and may be more appropriate for some exposures than the widely used threshold model[b].

Table 5
Sperm Parameters , Male Hormone Levels and Pesticide Exposure
(See Appendix F for explanation of the table)

Sperm Counts[(a)]	
Argentina farm 2,4-D users vs nonusers[118]	OR 0.49
Argentina farm pesticide exposure[119]	Decrease
Denmark farmers pre-pesticide exposure[120]	197 m/ml
Farmers post-pesticide exposure[(b)]	153 m/ml
Pre-exposure controls	223 m/ml
Post exposure controls[(b)]	178 m/ml
Denmark traditional farmers[121]	58 m/ml
Organic farmers	64 m/ml[#]
Internat. DBCP applicators[©] azoospermia[122]	64%
Israel post DBCP azoospermia - recovery[(d)78]	33%
Oligospermia - recovery[(d)]	50%
Philippines DBCP azo/oligospermia[121]	90%
US California DBCP median in exposed[123,124]	46 m/ml
Median in unexposed	79 m/ml
Azoospermia exposed[(e)]	13.1 %
Azoospermia unexposed	2.9 %
Oligospermia exposed	6.8 %
Oligospermia unexposed	0 %
Low normal count (20-39 m/ml) exposed	15.8 %
Low normal count (20-39 m/ml) unexposed	5.7%
US Hawaii papaya workers exposed EDB[(f)125]	81 m/ejac.
Unexposed	140 m/ejac.
US National molinate workers[(g)126]	No assoc.
US National DBCP workers (14 studies)[127]	107.1 m/ml
Median sperm count	83.0 m/ml
Men with sperm counts < 20 m/ml	8.7 %
US Virginia Kepone production workers[128,129]	Decrease
Sperm Characteristics	
Argentina farm 2,4-D motility (improved)[117]	OR 0.50
Necrospermia[(h)] (improved)	OR 2.25
Teratospermia[(h)] (persisted)	OR 2.16
China factory workers aneuploidy[(I)130]	RR 1.51
Pesticide exposed number/1,000 sperm	3.03
Unexposed number/1,000 sperm	1.94
Denmark farmers high expos. normal sperm[131]	60% decr.
Exposed 10 years vs less than 5 yrs	40% decr.
Low exposure, normal sperm	14% decr.
Finland fungicide use sperm aneuploidy[(j)132]	No assoc.
France infertile farm couple lindane use[106]	Case report
Sperm motility without/with protection	5% / 20%
Necrospermia[(h)] without/with protection	60% / 0%
Teratospermia[(h)] without protection	60%
Teratospermia[(h)] with protection	Persistent
US Hawaii EDB[(f)] viable sperm[124]	No assoc.
Teratospermia[(h)]	OR 1.69
US Iowa farmers semen parameters[133]	No assoc.
Hormone Levels	
Argentina farming area estradiol level[115]	Increase
China pesticide factory workers serum FSH[(k)134]	Increase[#]
Serum testosterone	Decrease[#]
Denmark organic farmers inhibin B[(I)120]	Higher
Organic testosterone SHBG[(m)] ratio	Higher
Denmark greenhouse testosterone:SHBG[(m)130]	Decrease
Germany testosterone chronic exposure[135]	Decrease
LH[(k)] after exposure	Increase
Germany vinclozolin[(n)] testosterone ng/m[136]	5.6 I[#]
Serum LH[(k)] IU/ml	9.0[#]
Serum FSH[(k)] mIU/ml	0.42 -4.9[#]
Israel 17 yr later FSH, LH[(k)]severely affected[78]	Increase
Testosterone	Decrease[#]
US California FSH[(k)] level azoospermics[121]	> 5.7mIU/ml
US lindane factory serum LH[(k)] gm. mean[137]	OR 1.53
Serum FSH[(k)]	Increase[#]
Serum testosterone	Decrease[#]
US MN herbicides post season FSH[(k)138]	Decrease
Herbicide use post season testosterone	Increased
Herbicide, insecticide, fumigant use	No assoc.
US National molinate workers[(g)] hormones[125]	No assoc.
US NC farmers hi DDE levels[(o)] testosterone[139]	22% lower

Not statistically significant

(**a)** Azoospermia is complete absence of sperm; oligospermia 20 million or less per milliliter of semen (m/ml). (**b)** Farmers not significantly different from controls. Post exposure drop was significant within each group **[c]** Exposed three years or more. (**d)** Recovery took 3-4 years after exposure ceased. (**e)** 2 had no DBCP exposure for 9 and 13 years; the first exposed for 4 yrs, the second for 2, both fathering children prior to exposure. (**f)** Ethylene dibromide, a fumigant similar to DBCP, and which also causes sterility. (**g)** 272 manufacturing /formulation workers at 3 plants. Mean exposure ranged from 12.7 to 210.9 ug/m^3 (**h)** Necrospermia: dead sperm. teratospermia: malformed sperm. (**I)** Abnormal number chromosomes. (**j)** Disomy /diploidy frequencies for chromosomes 1, 7. (**k)** Increased levels of LH (leutinizing hormone) and FSH (follicle-stimulating hormone) indicate testicular dysfunction. (**I)** Inhibin B is a sperm protein that correlates with sperm count. The higher the sperm count the higher inhibin B levels. (**m**) Sex hormone binding globulin binds testosterone.The higher the level of SHBG, the lower the amount of free (unbound) testosterone that is biologically active. (**n)** Factory workers exposed 1-13 years manufacturing/formulation operations.

[a] Attributed to Auroleus Phillipus Theostratus Bombastus von Hohenheim, known as 'Paracelsus,' a 16th century Dutch alchemist.
[b] Calabrese EJ, Baldwin LA. 2003. The hormetic dose-response model is more common than the threshold model in toxicology. Toxicolog Sci 71:246-250.

(**o)** Blacks who farmed about 30 years; 27% reported having used DDT. Testosterone level declined 1.9% per year of work.

Endocrine Disruptors:
Challengers to the "old toxicology" aver that it is not relevant to the fetus during critical periods of development in the first days and weeks of pregnancy. The fetus is especially vulnerable to low level contaminants that can adversely affect the endocrine system (glands which secrete hormones, including the pituitary, thyroid, adrenal, ovary, and testis). A recent book describes such contaminants as "endocrine disruptors", warning of potential harmful effects on the fetus of low level xenobiotics[c] such as plastics, phthalates, aklylphenols, pesticides, and other chemicals[d] . Many of these xenobiotics are estrogenic, mimicking the female hormone estrogen. See Appendix A for pesticides classified as endocrine disruptors.

Chlorinated Hydrocarbon Pesticides: Chlorinated hydrocarbons insecticides include DDT, DDE, aldrin, endrin, dieldrin, chlordane, heptachlor, hexachlorobenzene, lindane (hexachlorocyclohexane), and toxaphene. DDT was banned in 1972, aldrin and dieldrin in 1974, and chlordane in 1988. All were widely used in the 1950s and 1960s. They are still found in human tissues, especially those high in fat, because they degrade slowly, and are persistent in the environment. Even after two decades or more of non-use, many are still detectable. DDE is the metabolic breakdown product of DDT most commonly found in biological tissues.

Table 6
Sex Ratio and Pesticide Exposure
(See Appendix F for explanation of the table)

Canada National pesticide exposed[(b)] men[70]	No assoc.
Israel males conceived pre-exposure DBCP[(c)]	52.9 %
During exposure	35.2 %
After recovery	16.6 %
Turkey HCB[(d)] born to ♀ exposed 1955-57	Decrease [(e)]
Turkey boron high level villages[(f)] decrease	0.89
Low level villages no difference	1.04#
US California borate workers proportion males	Decrease#
US California DBCP water	No assoc.
US Minnesota pesticide applicators[2]	[0]0.75
Fungicide users	0.57
Subset of children with birth defects	1.75
US National molinate workers[(g)] births[125]	No assoc.

Not significant.
(a) A decrease in the ratio means more girls are born. **(b)** Thiocarbamates, carbaryl, other pesticides. **[c]** Dibromochloropropane, soil fumigant banned in 1979, known to cause sterility in men. **(d)** Hexachlorobenzene. 1950s outbreak of porphyria cutanea tarda from eating treated seed wheat not meant for consumption. **(e)** Lifetime spontaneous abortion rate predicted % males. **(f)**Two villages with high boron levels in drinking water (8.5-29mg/l, 2.05-2.5mg/l); three with low levels (0.03-0.40 mg/l). **(g)** Factory workers

Maternal and Paternal Pesticides (Table 7a)
Adipose Tissue (fat): The highest reported level of DDT in fat tissue of mothers at delivery (5900 ppb) was found in Kenyan women who also had high levels of β-HCH (30 ppb). Very high levels of DDE (4510 ppb) and DDT (1270 ppb) were found in adipose tissue of Mexican women at delivery.

Maternal Blood: The studies listed in Table 7 represent a selection from many studies of pesticides levels at delivery. The highest levels reported are 4450 ppm of DDE and 780 ppb of DDT in Mexican women.

In India, mothers who delivered stillborn babies had a 71% higher level of DDT in their serum than mothers with live births. There was no difference in lindane levels.

DDE was 260% higher in Israeli women who delivered premature babies than full term babies (71.1 vs 2.51 ppb), lindane 340% higher (15 vs 4.3 ppb), dieldrin 763% higher (8.4 vs 1.1 ppb), and heptachlor 303% higher (9.1 vs 3 ppb).

Low levels of DDE, trans-nonachlor and hexachlorobenzene were found in mothers in Greenland, and DDE and β-HCH in Japanese mothers.

Endosulfan and mirex were detected in 50% or more of

Pesticides Known to Cross the Placenta
(Selected List)

Acephate	DFP	Methyl paraoxon
Aldrin	Diazinon	Methyl parathion
Dieldrin	Dichlorvos	Methoxychlor
Apholate	Diquat	Mexacarbate
Benomyl	Formaldehyde	Mirex
Bromophos	Heptachlor	Nitrofen
Carbaryl	Hexachlorobenzene	Nicotine
Carbofuran	Imidan	Paraquat
Chlordane	Kepone	Parathion
Chlorpyrifos	Lindane	Pentachlorophenol
2,4-D	Malathion	Phosfolan
DDT	Mecarbam	2,4,5-T
DDE	Mephosfolan	TEPA
DDD	Methamidophos	Trichlorfon
Deet	Methiocarb	

Source: Salama AK, et al. 1993. A review article on placental transfer of pesticides. J Occ Med Toxicol 2(4):383-397.

[c] Pronounced zenobiotic, any biologically active substance not normally present or produced in the human body, and therefore foreign to it.
[d] Colburn T, Dumanoski D, Myers JP. *Our Stolen Future*. Dutton, New York. 1999.

samples from Canadian women undergoing in vitro fertilization. In the U.S., low levels of DDE were found in mothers in upstate New York, and in a national study, which also found a 500-310% increase in risk of pre-term births, and 90-260% increase in small for gestational age babies associated with DDE levels.

Two case reports from Poland in which women ingested pesticides to provoke abortion, found very high levels of carbofuran, and endosulfan in maternal blood. The mothers survived but the fetuses did not.

Ovarian Follicular Fluid:
Trace amounts of chlordane, DDE and hexachlorobenzene were found in follicular fluid from Canadian women undergoing in vitro fertilization (IVF). Another study found DDE and mirex in 50% or more of samples. Hexachlorobenzene and lindane (HCH) were found in the fluid of German women undergoing IVF.

Placenta
High levels in placenta were found in 1964-1965 samples from women living in a high agricultural production area of Californian . In India placental levels of DDT and lindane (HCH) from stillborn babies were not significantly different from live births. DDE and β-HCH were found in Japanese women in samples from the 1970s. A study in Mexico found that pesticide exposure increased the prevalence of atypical placental villi.

Semen:
Five ppb or more of 2,4-D was found in 50% of seminal fluid samples in Canadian farmers. Detectable levels of hexachlorobenzene, lindane, DDT, and dieldrin were found in German men, with the highest levels in chemistry students[162]. DDE, aldrin, endosulfan, and isomers of hexachlorocyclohexane (α-β-,γ-,δ -), were detected in men in India[163], and DDE and ϵ-HCH in Poland**.**

Testes:
In Greece, autopsies of suicides who died from ingesting pesticides found 21 ppb of paraquat, 5.8 ppb of fenthion and 0.8 ppm of methadithion in the testes.

Testicular Pathology:
Testicular biopsies in DBCP exposed workers show the seminiferous tubules to be the site of damage. Biopsies of ten severely affected California workers found seminiferous tubules devoid of spermatagonia and spermatogenic activity, resembling a Sertoli cell only syndrome. In the less severely affected, a decrease in cellularity was found within the seminiferous tubules without inflammation and only minimal evidence of an increase in fibrosis and interstitial changes. An early report of biopsies in severely affected Israeli DBCP workers found selective atrophy of the germinal epithelium, with the great majority of tubules lined only by Sertoli cells, and no evidence of active spermatogenesis. Large groups of leydig cells were present in the interstitial tissue surrounding the damaged tubules[168]. Biopsies done eight years later in Israeli workers exposed to DBCP for 100 to more than 6,000 hours, not all of whom had clinical signs of testicular dysfunction, found selective atrophy of the germinal epithelium, intact Sertoli cells, and a normal appearance of a relatively increased number of Leydig cells

Endometriosis:
A study of infertile women in German found an association between endometriosis and elevated levels of chlorinated hydrocarbon pesticides[140]. No association was found in wives of pesticide applicator in Minnesota, or with levels of chlorinated hydrocarbon pesticides in infertile women in Canada[141]. A review of chlorinated hydrocarbon pesticides includes a discussion of endometriosis[142].

Amniotic Fluid: A study done in Florida at a time of heavy agricultural DDT use found 14 ppb in black babies and 6 ppb in whites. A recent study found low levels of DDE and α-hexachlorocyclohexane in California women in their second trimester of pregnancy.

Meconium: Meconium is the intestinal contents of a newborn baby, and is the first “bowel movement”. It is an accumulation of intestinal epithelial cells, mucus, and bile. A 1971 study in Japan found DDE, DDT, dieldrin, and α-β-γ-HCH isomers. Two recent studies in Australia and the Phillipines tested for chlorinated hydrocarbon and organophosphate pesticides in the same laboratory, and is one few reporting pentachlorophenol. The amounts were

Table 7-A
Maternal and Paternal Fluids and Tissues
and Pesticide Contamination / Exposure

Adipose Tissue (Fat)	
Kenya total DDT mother at delivery[143]	5900 ppb
β-HCH[(b)]	30 ppb
Mexico DDE mother at delivery[144]	4510 ppb
DDT mother at delivery	1270 ppb
Maternal Blood at Delivery	
Canada IVF[(a)] DDE , endosulfan, mirex[100] detected	>50%
Greenland DDE[145]	4.8 ppb
Trans-nonachlor	1.6 ppb
Hexachlorobenzene	1.2 ppb
India 1983 DDT total stillbirth[146]	96.8 ppb
DDT total live birth	26.2 ppb*
HCH[(b)] stillbirth	17.3 ppb
HCH[(b)] live birth	18.3 ppb#
Israel 1982 DDT premature births[147]	71.10 ppb
DDT term births	26.51 ppb
Lindane premature births	15.0 ppb
Lindane term births	4.30 ppb
Dieldrin premature births	8.40 ppb
Dieldrin term births	1.10 ppb
Heptachlor premature births	9.10 ppb
Heptachlor term births	3.00 ppb
Japan 1976 β-HCH[148]	1.9 ppb
DDE	11.5 ppb
Japan 1974 samples β-HCH[(b)149]	7.7 ppb
DDE 1974 samples	4.7 ppb
Mexico 1994 DDE at delivery[148]	4450 ppb
DDT	780 ppb
Poland ingestion[©)] poisoning carbofuran[150]	9710 ppb
Endosulfan ingestion[©)] poisoning	470 ppb
US California farm workers cholinesterase[151]	Decrease
US CPP[(d)] DDE median (range 3-178)[152]	25 ppb
DDE and pre-term births	OR 1.5-3.1
DDE and small for gestational age	OR 1.9-2.6
US New York State DDE[153]	3.8 ppb
Ovarian Follicular Fluid	
Canada chlordane, DDE, HCB[ed)] IVF[(a)101]	Trace
Canada DDE, Mirex IVF[(a)] samples detected[100]	≥50%
Germany IVF HCB[(d)154]	0.08-1.87ppb
HCH[(b)]	0.05-1.0 ppb
Placenta	
India DDT total stillbirth[150]	60.8 ppb
DDT (total) live birth	39.8 ppb
HCH[(b)]stillbirth	13.4 ppb
HCH[(b)] live birth	17.1 ppb
Japan 1976 samples β-HCH[(b)152]	6.8 ppb
DDE	4.3 ppb
Japan 1974 samples β-HCH[(b)153]	5.7 ppb
DDE samples	3.2 ppb
Mexico atypical placental villi[155]	Increase
US California 1965 samples fat basis DDE[156]	5000 ppb
Semen	
Canada Ont. farmers 2,4-D 50% of samples[157]	≥5 ppb
Germany HCB[(e)], HCH[(b)], DDT, dieldrin[158]	Detected
Chemistry students	Elevated
India general population OCl[(f)159]	Detected
Poland general population ϵ-HCH[(b)160]	500 ppb
DDE in 40% samples	3 ppb
Testes	
Greece poisoning paraquat (autopsy)[161]	21 ppb
Greece poisoning fenthion(autopsy)[162]	5.9 ppb
Methidathion	0.8 ppb
Testicular Biopsy	
Israel DBCP exposed workers 1986 samples[163]	Abnormal
Israel DBCP severe effects 1978 samples[164]	Abnormal
US DBCP severe effects 1978 samples[122]	Abnormal

* Difference statistically significant .
\# Difference not significant
ppb parts per billion = ug/kg, ug/l, ng/g, ng/ml, pg/ml

(a) In vitro fertilization.**(b)** Hexachlorocyclohexane. Lindane is the gamma (γ-) isomer. **[c]** With the intent to provoke an abortion. Women survuved, fetuses died. **(d)** Collaborative Perinatal Project, a cohort study from 1959-1965 of pregnant women and their children at 12 medical centers (about 56,000 pregnancies). **(e)** Hexachlorobenzene. **(f)** OCl: organoclorine pesticides includies DDT, dieldrin, lindane, hexachlorobenzene, chlordane, and others.

much higher in the Filipino babies for all the pesticides found. The organophosphate pesticides diazinon and parathion were found only in the Filipinos. See Table 7a for the specific pesticides and amounts found. A study done in Germany found DDE in 5% of samples collected in 1997. A study in New York found several biomarkers of organophosphate pesticides. The findings represent recent exposures since organophosphate pesticide are not persistent and are rapidly eliminated from the body. Widely used organophoshates include chlorpyrifos, diazinon, malathion, methyl parathion, acephate and others[180].

Umbilical Cord Blood:
The presence of pesticides in cord blood is evidence of transplacental passage. Most tests of maternal/fetal pairs are for persistent pesticides in the DDT family. The highest reported level of DDE was found in Mexican babies born in

1997 (4700 ppb), and DDT levels were also high (880 ppb). The highest level of hexachlorobenzene (HCB) was reported in 1985 from Tunisia (37 ppb) where use was widespread in agriculture; much lower levels were found in babies in Nicaragua (6.39 ppb), in Spanish babies born 1997 to 1999 (1.1 ppb) and in German babies born in 1994 (0.5 ppb). High levels of DDT and lindane were found in stillborn babies in India but the levels were not were not significantly from full term births[150]. In the U.S., low levels of DDE were found in infants born from 1993 to 1998 in Massachusetts[191], and trace amounts of DDE, DDT and endosulfan in Texas farm workers[192]. In Canada, low levels of DDE were found in infants born in 1994 to 1999, and significant decreases in DDT, DDE, hexachlorobenzene and chlordane from 1993 to 2000.

There are racial differences in DDE levels in cord blood. A 1970 study in Florida found a 23% higher level of DDE in the whole blood of black infants than white, and a 1972 study a 22% higher level of DDE in cord blood of full term black infants than whites.

No reports of organophosphate pesticides in cord blood were found. Studies in California and Florida found decreased cholinesterase activity, a biomarker of organophosphate exposure. Since these pesticides are not persistent, the findings reflect recent exposure.

Another pesticide found in cord blood is the widely used insect repellent deet. In a study in Thailand deet was found in 8% of babies whose mothers used the repellent in the second and third trimester of pregnancy.

Umbilical Cord Tissue: A study in the Faroe Islands found DDE and hexachlorobenzene in umbilical cord tissue[193].

Sudden Infant Death Syndrome (SIDS)
A study in Germany found no difference in pentachlorophenol levels at autopsy in children who died of SIDS compared to controls, or in children from rural versus urban areas[165]. Another German study found no significant differences in the levels of hexachlorbenzene, or α-,β-,γ-isomers of hexachlorcyclohexane, heptachlor epoxide, dieldrin, and total DDT in the subcutaneous fat of children who died of SIDS compared to children who died of known causes[166].

Developmental Disabilities
There are no studies of pesticides as a risk factor for developmental disabilities in children such as autism, cerebral palsy, and severe mental retardation, although research interest is increasing.

Table 7-B
Fetal and Infant Fluids and Tissues and Pesticides Residues

Adipose Tissue (Fat)		
Germany fetus, autopsy DDT[167]		700 ppb
HCH[(a)] fetus, autopsy		140 ppb
Heptachlor fetus, autopsy		30 ppb
Germany HCB[(b)] children cryptorchidism[168]		Increased
Heptachlor epoxide		Increased
Great Britain DDT premature infants[169]		960 ppb
DDE 1 day to 3 months		720 ppb
Amniotic Fluid		
US California 2nd trimester[(c)] DDE[170]		0.21 ppb
α-HCH[(a)]		0.15 ppb
US Florida DDE black infants[171]		14 ppb
DDE white infants		6 ppb
Meconium[(d)]		
Australia[172]	Detected	Mean
Lindane wt < 2500 grams	100%	0.2 ppt
Weight > 2500 grams	57%	0.06 ppt
Pentachlorophenol	43%	8.0 ppt
Chlordane	16%	0.23 ppt
DDT	52%	0.04 ppt
Chlorpyrifos[(e)]	59%	0.52 ppt
Malathion	35%	0.052 ppt
Diazinon, parathion	Not detected	
Germany DDE samples detected[173]	5%	-
Japan DDE, dieldrin[174]		9 ppb
DDT		12 ppb
Total HCH[(a)]		30 ppb
Philippines Manila[175]	Detected	Mean
Lindane	73.5%	2.0 ppt
Pentachlorphenol	16.1%	90.0 ppt
Chlordane	12.7%	22.48 ppt
DDT	26.5%	12.56 ppt
Chlorpyrifos	11.0%	8.26 ppt
Malathion	53.0	6.80 ppt
Diazinon	34.3%	12.96 ppt
Parathion	32.0%	2.30 ppt
US New York OP[(f)] metabolites[176]	Detected	Mean
DEP	95%	0.8-3.2 ug/g
DETP	100%	2.0-5.6 ug/g
DMP	5%	16.0 ug/g
DEDTP	5%	1.8 ug/g

Umbilical Cord blood	
Canada Que. DDE 1994-99 samples[177]	0.412 ppb
Canada Que. chlordane decrease 1993-2000[178]	25%
DDT/DDE decrease 1993-2000	66%
HCB[(b)] decrease 1993-2000	69%
Germany HCB[(b)] 1994 (90% decrease)[179]	0.5 ppb
India 1983 total DDT stillbirths[150]	33.6 ppb
Total DDT live births	30.9 ppb
HCH[(a)] stillbirths	14.8 ppb
HCH[(a)] live births	13.6 ppb
Japan 1976 samples β-HCH[152]	5.7 ppb
DDE	5.5 ppb
Japan 1974 samples β-HCH[153]	1.9 ppb
DDE	1.8 ppb
Kenya 1976 total DDT[147]	1.9 ppm
Mexico 1997-98 samples DDE[148]	4700 ppb
DDT	880 ppb
Nicaragua 1990s samples DDE[180]	6.39 ppb
Spain 1997-99 samples HCB[(b)][181]	1.1 ppb
DDE, β-HCH[(a)]	Detected
Thailand deet use 2nd, 3rd trimester[182]	8% samples
Tunisia 1985 samples HCB[(b)][183]	37 ppb
US California RBC cholinesterase[(g)] decrease[184]	53%
US Florida 1972 DDE premature black[(h)][185]	19.0 ppb
DDE premature white[(h)]	22.1 ppb
DDE full term black[(h)]	6.1 ppb
DDE full term white[(h)]	4.9 ppb
US Florida 1970 DDE black infants[174]	5.9 ppb
DDE white infants	4.8 ppb
US Florida low cholinesterase activity[(g)][186]	0.59ΔpH[(i)]
US Massachusetts DDE[187]	0.48 ppb
HCB[(b)]	0.03 ppb
US New York State DDE[157]	1.9 ppb
US Texas DDE/DDT, endosulfan farm wkrs[188]	Detected
Umbilical Cord Tissue	
Faroe Islands DDE whole weight[189]	0.17 ppb
HCB[(b)] whole weight	1.19 ppb

* statistically significant difference # difference not significant
ppm parts per million = mg/kg, ug/g, mg/l, ug/ml
ppb parts per billion = ug/kg, ug/l, ng/g, ng/ml, pg/ml
ppt parts per trillion = ug/ml, ng/kg, ng/l, pg/m l

(a) Hexachlorocyclohexane. Lindane is the gamma isomer. **(b)** Hexachlorobenzene **[c]** One in three samples tested positive for at least one contaminant. **(d)** The intestinal contents of a newborn baby. Te first "bowel movement" after delivery it is dark green and consists of intestinal epithelial cells, mucus, and bile. **(e)** Not detected in 3 babies from Cairns and Mackay, despite heavy agricultural use in those regions **(f)** Organophosphate metabolites: biomarkers of recent exposure to several widely used pesticides including chlorpyrifos, diazinon, malathion, acephate, merhyl parathion, and others. DEP = O,O-diethylphos-phate, DETP = O,O-diethyldithiophosphate, DMP = O,O-dimethylphos-phate; DEDTP = O,O-diethyldithio-phosphate. **(g)** Biomarker of organophosphate pesticide exposure. **(h)** Infant whole blood, not from cord. **(i)** Normal is 1.9 or greater.

References

1. Whyatt RM, et al. 2003. Contemporary-use pesticides in personal air samples during pregnancy and blood samples at delivery among urban minority mothers and newborns. Env Health Persp 111:749-756.
2. White FMM, et al 1988. Chemicals, birth defects and stillbirths in New Brunswick: associations with agricultural activity. Can Med Assoc J 138:117-124.
3. Rojas A, et al. 2000. [Congenital malformations and pesticide exposure]. Rev Med Chil 128(4):399-404.
4. Pan XQ. 1994. [Analysis of the combined effects of exposure to multiple pesticides on fetal development]. Huan Ching Ko Hsueh 15(1):73-74.
5. Restrepo M, et al. 1990. Birth defects among children born to a population occupationally exposed to pesticides in Columbia. Scand J Work Env Health 16:239-246.

6. Restrepo M, et al. 1990. Prevalence of adverse reproductive outcomes in a population occupationally exposed to pesticides in Colombia. Scand J Work Env Health 16:232-238.
7. Nurminen T, et al. 1995. Agricultural work during pregnancy and selected structural malformations in Finland. Epidemiology 6(1):23-30.
8. Czeizel AE. 1996. Pesticides and birth defects [letter]. Epidemiology 7(1):111.
9. Rupa DS, et al. 1991. Reproductive performance in population exposed to pesticides in cotton fields in India. Env Res 55(2) :123-128.
10. Bajaj JS, et al. 1993. Environmental release of chemicals and reproductive ecology. Env Health Persp 101(Suppl 2):125-130.
11. Hanify JA, et. al. 1981. Aerial spraying of 2,4,5-T and human birth malformations: an epidemiological investigation. Science 212:349-351.
12. Smith AH, et al. 1982. Congenital defects and miscarriages among New Zealand 2,4,5-T sprayers. Arch Env Health 37:197-200.
13. Irgens A, et al. 2000. Birth defects and paternal occupational exposure. Hypotheses tested in a record linkage based dataset. Acta Obs Gyn Scand 79(6):465-470.
14. Crisostomo L, et al. 2002. Pregnancy outcomes among farming households of Nueva Ecija with conventional pesticide use versus integrated pest management. Int J Occ Env Health 8(3):232-242.
15. Garcia AM, et al. 1999. Parental agricultural work and selected congenital malformations. Am J Epid 149(1):64-74.
16. Garcia AM, et al. 1998. Paternal exposure to pesticides and congenital malformations. Scand J Work Env Health 24(6):473-480.
17. Bell et al. 2001. A case-control study of pesticides and fetal death due to congenital anomalies. Epidemiology 12(2):148-156.
18. Grether JK, et. al. 1987. Exposure to aerial malathion application and the occurrence of congenital anomalies and low birthweight. Am J Pub Health 77:1009-1010.
19. Rappolt RT, et al. 1968. Kern County: Annual generic pesticide input; blood dyscrasias; p,p'- DDE and p,p'-DDT residues in human fat, placentas with related stillbirths and abnormalities Ind Med Surg 37(7):513.
20. LeMarchand L, et al. 1986. Trends in birth defects for a Hawaiian population exposed to Heptachlor and for the United States. Arch Env Health 41:145-148.
21. Garry VF, et al. 1996. Pesticide appliers, biocides, and birth defects in rural Minnesota. Env Health Persp 104(4):394-399.
22. Casey PH, et al.1984. Severe mental retardation and multiple congenital anomalies of uncertain cause after extreme parental exposure to 2,4-D. J Pediatrics 104:313-315.
23. Jeandel C, et al. 2001. Environmental disruptors as possible cause of ambiguous genitalia in three male newborns. Ped Res 49(6 Pt 2):57A
24. Schaefer C, et al. 1992. Intrauterine diethyltoluamide exposure and fetal outcome. Repro Toxicol 6(2):175-176.
25. Lindhout D, et al. 1987. Amyoplasia congenita-like condition and maternal malathion exposure. Teratology 36:7-9.
26. Romero P, et al. 1989. Congenital anomalies associated with maternal exposure to oxydemeton-methyl. Env Res 50:256-261.
27. Rantala K, et al. 1987. Major birth defects and pesticide exposure in Finland. Scand J Work Env Health 13(2):159.
28. Kristensen P, et al. 1997. Birth defects among offspring of Norwegian farmers, 1967-1991. Epidemiology 8(5):537-544.
29. Bradley CM, et al. 1995. Parental occupations as risk factors for craniosynostosis in offspring. Epidemiology 6(3):306-310.
30. Garry VF, et al. 2002. Birth defects, season of conception, and sex of children born to pesticide applicators living in the Red River Valley of Minnesota, USA. Env Health Persp 110(Suppl 3):441-449.
31. Fixler DE, et al. 1998. Prenatal exposures and congenital heart defects in Down syndrome infants. Teratology 58(1):6-12.
32. Balarajan R, et al. 1983. Congenital malformations and agricultural workers. Lancet 1:1112-1113.
33. Golding J, et al. . 1983. Congenital malformations and agricultural workers. (Letter). Lancet 1:1393.
34. Nelson CJ, et al. 1979. Retrospective study of the relationship between agricultural use of 2,4,5-T and cleft palate occurrence in Arkansas. Teratology 19(3):377-384.
35. Shaw GM, et al. 1999. Maternal pesticide exposure from multiple sources and selected congenital anomalies. Epidemiology 10(1):60-66.
36. Schnitzer PG, et al. 1995. Paternal occupation and risk of birth defects in offspring. Epidemiology 6(6):577-583.
37. Gordon JE, et al. 1981. Agricultural chemical use and congenital cleft lip and/or palate. Arch Env Health 36:213-221.
38. Wang J, et al. 2002. Study on risk factors of cryptorchidism.. Zhonghua Liu Xing Bing Xue Za Zhi. 23(3):190-193.
39. Weidner IS, et al. 1998. Cryptorchidism and hypospadias in sons of gardeners and farmers. Env Health Persp 106(12):793-796.
40. Longnecker MP, et al. 2002. Maternal serum level of 1,1-dichloro-2,2-bis(p- chloro phenyl)ethylene and risk of cryptorchidism, hypospadias, and polythelia among male offspring. Am J Epid 155(4):313-322.
41. Dimich-Ward H, et al. 1996. Reproductive effects of paternal exposure to chlorophenate wood preservatives in the sawmill industry. Scand J Work Env Health 22:267-273.
42. Olshan AF, et al. 1991. Paternal occupation and congenital anomalies in offspring. Am J Ind Med 20(4):447-475.
43. Dolk H, et al. 1998. Geographical variation in anophthalmia and microphthalmia in England, 1988-94. Brit Med J 317:905-909.
44. Spagnolo A, et al. 1994. Anophthalmia and benomyl in Italy: A multicenter study based on 940,615 newborns. Reprod Toxicol 8(5):397-403.
45. McDonald AD, et al. 1988. Congenital defects and work in pregnancy. Br J Ind Med 45(9):581-588.
46. Thomas DC, et al. 1992. Reproductive outcomes in relation to malathion spraying in the San Francisco Bay Area, 1981-1982. Epidemiology 3(1):32-39.
47. Tikkanen J, et al. 1994. Risk factors for hypoplastic left heart syndrome. Teratology 50(2) :112-117.
48. Tikkanen J, et al. 1992. Risk factors for atrial septal defect. Eur J Epid 8(4):509-515.
49. Tikkanen J, et al, 1991. Risk factors for ventricular septal defect in Finland. Public Health 105(2):99-112
50. Loffredo et al. 2001. Association of transposition of the great arteries in infants with maternal exposures to herbicides and rodenticides. Am J Epid 153(6):529-536.
51. Wilson PD, et al. 1998. Attributable fraction for cardiac malformations. Am J Epid 148(5):414-423.
52. Correa-Villaseñor A, et al. 1991. Total anomalous pulmonary venous return: familial and environmental factors. Teratology 44:415-428.
53. Kricker A, et al. 1986. Women and the environment: a study of congenital limb anomalies. Com Health Stud 10:1-11.
54. Schwartz DA, et al. 1988. Congenital limb reduction defects in the agricultural setting. Am J Pub Health 78:654-657.
55. Schwartz DA, et al. 1986. Parental occupation and birth outcome in an agricultural community. Scand J Work Env Health 12:51-54.
56. Roan CC, et al. 1984. Spontaneous abortions, stillbirths, and birth defects in families of agricultural pilots. Arch Env Health 39:56-60.
57. Lin S, et al. 1993. Evaluation of congenital limb reduction defects in upstate New York. Teratology 47(2):127-135.
58. Engel LS, Oet ak, 2000. Maternal occupation in agriculture and risk of limb defects in Washington State, 1980-1993. Scand J Work Env Health 26(3):193-198.
59. Zhang J, et al. 1992. Occupational hazards and pregnancy outcomes. Am J Ind Med 21(3):397-408.
60. Berry RJ, et al. 1999. Prevention of neural-tube defects with folic acid in China. N Eng J Med 341(20):1485-1490.

61. Blatter BM, et al. 2000. Spina bifida and parental occupation: results from three malformation monitoring programs in Europe. Eur J Epid 16(4):343-351.
62. Blatter BM, et al. 1996. Spina bifida and parental occupation. Epidemiology 7(2):188-193.
63. Blatter BM, et al. 1996. Maternal occupational exposure during pregnancy and the risk of spina bifida. Occ Env Med 53(2):80-86.
64. Blatter BM, et al. 1997. Paternal occupational exposure around conception and spina bifida in offspring. Am J Ind Med 32(3):283-291.
65. Blatter BM, et al. 1996. Spina bifida and parental occupation in a Swedish register-based study. Scand J Work Env Health 22(6):433-437.
66. Hearey CD, et al. 1984. Investigation of a cluster of anencephaly and spina bifida. Am J Epid 120(4):559-564.
67. Brender JD, et al. . 1990. Paternal occupation and anencephaly. Am J Epid 131:517-521.
68. Brender J, et al. 2002. Parental occupation and neural tube defect-affected pregnancies among Mexican Americans. Occ Env Med 44(7):650-656.
69. Marinova G, et al. 1973. Professional injuries of pesticides and their effects on the reproductive functions of women working with pesticides. Akush. Ginekol (Sofiia) 12:138-140.
70. Arbuckle TE, et al. 2001. An exploratory analysis of the effect of pesticide exposure on the risk of spontaneous abortion in an Ontario farm population. Env Health Persp 109(8):851-857.
71. Arbuckle TE, et al. 1999. Exposure to phenoxy herbicides and the risk of spontaneous abortion. Epidemiology 10(6):752-760.
72. Savitz DA, et al. 1997. Male pesticide exposure and pregnancy outcome. Am J Epid 146(12):1025-1036.
73. McDonald AD, et al. 1988. Fetal death and work in pregnancy. Br J Ind Med. 45:148-157.
74. Heidam LZ.1984. Spontaneous abortions among dental assistants, factory workers, painters, and gardening workers. J Epid Comm Health 38:149-155.
75. Hemminki K, et al. 1982. Spontaneous abortions in hospital staff engaged in sterilising instruments with chemical agents. Br Med J 285(6353):1461-1463.
76. Gerhard I, et al. 1998. Chlorinated hydrocarbons in women with repeated miscarriages. Env Health Persp 106(10):675-681.
77. Varma Dr. 1987. Epidemiological and experimental studies on the effects of methyl isocyanate on the course of pregnancy. Env Health Persp 72:153-158.
78. Rita P, et al. 1987. Monitoring of workers occupationally exposed to pesticides in grape gardens of Andhra Pradesh. Env Res 44:1-5.
79. Potashnik G, et al. 1995.DBCP: a 17-year reassessment of testicular function and reproductive performance. J Occ Env Med 37(11):1287-1292.
80. Goldsmith JR, et al. 1984. Reproductive outcomes in families of DBCP-exposed men. Arch Env Health 39:85-89.
81. Kharrazi M, et al. 1980. Reproductive effects of dibromochloropropane. Israel J Med Sci 16:403-406.
82. Petrelli G, et al. 2000. Reproductive male-mediated risk: spontaneous abortion among wives of pesticide applicators. Eur J Epid 16(4):391-393.
83. Leoni V, et al. 1986. Spontaneous abortion in relation to the presence of hexachlorobenzene in the Italian environment . IARC Sci Pub 77:143-146.
84. Kristensen P, et al. 1997. Gestational age, birth weight, and perinatal death among births to Norwegian farmers, 1967-1991. Am J Epid 146(4):329-338.
85. Parron T, et al. 1996. Clinical and biochemical changes in greenhouse sprayers chronically exposed to pesticides. Hum Exp Toxicol 15(12):957-963.
86. Jarrell J, et al. 1998. Evaluation of reproductive outcomes in women inadvertently exposed to hexachlorobenzene in Southeastern Turkey in the 1950s. Repro Toxicol 12(4):469-476.
87. Rowland AS, et al. 1996. Ethylene oxide exposure may increase the risk of spontaneous abortion, preterm birth,and postterm birth. Epidemiology 7(4):363-368.
88. O'Leary Jaet al. 1970. Spontaneous abortion and human pesticides residues of DDT and DDE. Am J Obst Gynecol 108:1291-1292.
89. Garry VF, et al. 2002. Reproductive outcomes in the women of the Red River Valley of the north. Part I.. J Toxicol Env Health A 65(11):769-786.
90. Goulet L, et al. 1991. Stillbirth and chemical exposure of pregnant workers. Scand J Work Env Health 17(1):25-31.
91. Goulet L, et al. 1989. Stillbirth and chemical exposure of pregnant workers. Am J Epid 130(4):835.
92. Taha TE, et al. 1993. Agricultural pesticide exposure and perinatal mortality in central Sudan. Bull WHO 71(3-4):317-321.
93. Bell EM, et al. 2001. Case-cohort analysis of agricultural pesticide applications near maternal residence and selected causes of fetal death. Am J Epid 154(8):702-710.
94. Pastore LM, et al. 1997. Risk of stillbirth from occupational and residential exposures. Occ Env Med 54(7):511-518.
95. Aschengrau A, et al. 1989. Quality of community drinking water and the occurrence of spontaneous abortion. Arch Env Health 44:283-290.
96. Savitz DA, et al. 1989. Self-reported exposure to pesticides and radiation related to pregnancy outcome. Pub Health Rep 104:473-477.
97. Hourani L, et al. 2000. Occupational and environmental exposure correlates of adverse live-birth outcomes among 1032 US Navy women. J Occ Env Med 42(12):1156-1165.
98. Ihrig MM, et al. 1998. A hospital-based case-control study of stillbirths and environmental exposure to arsenic using an atmospheric dispersion model linked to a geographical information system. Epidemiology 9(3):290-294.
99. Vaughan TL, et al. 1984. Fetal death and maternal occupation: an analysis of birth records in the state of Washington. J Occ Med 26:676-678.
100. Strohmer H, et al. 1993. Agricultural work and male infertility. Am J Ind Med 24(5):587-592.
101. Younglai EV, et al. 2002. Levels of environmental contaminants in human follicular fluid, serum, and seminal plasma of couples undergoing in vitro fertilization. Arch Env Cont Toxicol 43(1):121-126.
102. Jarrell JF, et al. 1993. Contamination of human ovarian follicular fluid and serum by chlorinated organic compounds in three Canadian cities. Can Med Assoc J 148(8):1321-1327.
103. Curtis KM, et al. 1999. The effect of pesticide exposure on time to pregnancy. Epidemiology 10(2):112-117.
104. Heacock H, et al. 1998. Fertility among a cohort of male sawmill workers exposed to chlorophenate fungicides. Epidemiology 9(1):56-60.
105. Smith EM, et al. 1997. Occupational exposures and risk of female infertility. J Occ Env Med 39(2):138-147.
106. Abell A, et al. 2000. Time to pregnancy among female greenhouse workers. Scand J Work Env Health 26(2):131-136.
107. Larsen SB, et al. 1998. Time to pregnancy and exposure to pesticides in Danish farmers. Occ Env Med 55(4):278-283.
108. Thonneau P, et al. 1999. Effects of pesticide exposure on time to pregnancy: Am J Epid 150:157-163
109. Espir MLE, et al 1970. Impotence in farm workers using toxic chemicals. Br Med J 1:423-425.
110. Cranz C. 1981. [A case of reversible sterility probably due to intoxication by lindane]. Contacep Fertil Sexual 9:421-423.
111. Petrelli G, et al. 2001. [Occupational exposure and male fertility. Results of an Italian multicenter study in an exposed population]. Med Lav 92(5):307-313.
112. Petrelli G, et al. 2000. [Exposure to pesticides in greenhouses and male fertility]. G Ital Med Lav Ergon 22(4):291-295.
113. Tielemans E, et al. 1999. Pesticide exposure and decreased fertilization rates in vitro. Lancet 354(9177):484-485.
114. DeCock J, et al. 1994. Time to pregnancy and occupational exposure to pesticides in fruit growers in The Netherlands Occ Env Med 51(10):693-699.
115. Whorton MD, et al. 1979. Testicular function among carbaryl exposed employees. J Toxicol Env Health 5:929-941.
116. Glass R, et al. 1978. The gonadal toxicity of DBCP among male pesticide applicators. Am J Epid 108(3):242.
117. Fuortes L, Clark MK, Kirchner HL, et al. 1997. Association between female infertility and agricultural work history. Am J Ind Med 31(4)445-451.
118. Lerda D, et al. 1991. Study of reproductive function in persons occupationally exposed to 2,4-dichlorophenoxy-acetic acid (2,4-D). Mutat Res 262:47-50.

119. Oliva A, et al. 2001. Contribution of environmental factors to the risk of male infertility. Hum Reprod. 16(8):1768-1776.
120. Larsen SB, et al. 1998. A longitudinal study of semen quality in pesticide spraying Danish farmers. Repro Toxicol 12(6):581-589.
121. Larsen SB, et al. 1999. Semen quality and sex hormones among organic and traditional Danish farmers. Occ Env Med 56(2):139-144.
122. Slutsky M, et al.1999. Azoospermia and oligospermia among a large cohort of DBCP applicators in 12 countries. Int J Occ Env Health 5(2):116-122.
123. Whorton D, et al. 1979. Testicular function in DBCP exposed pesticide workers. J Occ Med 21:161-166.
124. Whorton D, et al. 1977. Infertility in male pesticide workers. Lancet 2(8051):1259-1261.
125. Ratcliffe JM, et al. 1987. Semen quality in papaya workers with long term exposure to ethylene dibromide. Br J Ind Med 44:317-326.
126. Tomenson JA, et al. 1999. An assessment of fertility in male workers exposed to molinate. J Occ Env Med 41(9):771-787.
127. Whorton D, et al. 1984. Sperm count results from 861 American chemical and agricultural workers from 14 separate studies. Ferti Steril 42:82-86.
128. Cannon SB, Jackson RS, et al. 1978. Epidemic kepone poisoning in chemical workers. Am J Epid 107:529-537.
129. Reich MR, 1983. Kepone: a chemical disaster in Hopewell, Virginia. Int J Health Serv 13(2):227-246.
130. Padungtod C, et al. 1999. Sperm aneuploidy among Chinese pesticide factory workers: scoring by the FISH method. Am J Ind Med 36(2):230-238.
131. Abell A, et al. 2000. Semen quality and sexual hormones in greenhouse workers. Scand J Work Env Health 26(6):492-500.
132. Harkonen K, et al. 1999. Aneuploidy in sperm and exposure to fungicides and lifestyle factors. Env Mol Mutag 34(1):39-46.
133. Gerber WL, et al. WC. 1988. Infertility, chemical exposure, and farming in Iowa: absence of an association. Urology 31:46-50.
134. Padungtod C, et al. 1998. Reproductive hormone profile among pesticide factory workers. J Occ Env Med 40(12):1038-1047.
135. Straube E, et al. 1999. Disruption of male sex hormones with regard to pesticides. Toxicol Lett 107(1-3):225-231.
136. Zober A, et al. 1995. Study of morbidity of personnel with potential exposure to vinclozolin. Occ Env Med 52(4):233-241.
137. Tomczak S, et al. 1981. Occupational exposure to hexachlorocyclohexane. IV. Sex hormone alterations. Int Arch Occ Env Health 48(3):283-287.
138. Garry VF, et al. 1999. Herbicides and adjuvants: an evolving view. Toxicol Ind Health 15(1-2):159-167.
139. Martin SA Jr, et al. 2002. DDT metabolite and androgens in African-American farmers. Epidemiology 13(4):454-458.
140. Gerhard I, et al. 1998. Chlorinated hydrocarbons in infertile women. Env Res 80(4):299-310.
141. Lebel G, et al. 1998. Organochlorine exposure and the risk of endometriosis. Fertil Steril 69(2):221-228.
142. Ahlborg UG, et al. 1995. Organochlorine compounds in relation to breast cancer, endometrial cancer, and endometriosis. Crit Rev Toxicol 25(6):463-531.
143. Kanja LW, et al. 1992. A comparison of organochlorine pesticide residues in maternal adipose tissue, maternal blood, cord blood, and human milk from mother/infant pairs. Arch Env Contam Tox 22:21-24.
144. Waliszewski SM, et al. 2000. Carry-over of persistent organochlorine pesticides through placenta to fetus. Salud Publica Mex 42(5):384-390.
145. Bjerregaard P, et al. 2000. Organochlorines and heavy metals in pregnant women from the Disko Bay area in Greenland. Sci Total Env 245(1-3):195-202.
146. Saxena MC, et al. 1983. A comparison of organochlorine insecticide contents in specimens of maternal blood, placenta, and umbilical-cord blood from stillborn and live-born cases. J Toxicol Env Health 11:71-79.
147. Wassermann M, et al. 1982. Premature delivery and organochlorine compounds. Env Res 28:106-112.
148. Uchida Wakatsuki S. 1976. [Results of survey on pesticides in human body.] Nippon Noson Igakkai Zasshi (J. Jpn Assoc Rural Med) 25(1):47-48.
149. Takamiya T,1975. [Organochlorine pesticide residues in human placenta and blood]. Jpn. Assoc. Rural Med.) 24(3):430-431.
150. Sancewicz-Pach K, et al. 1997. Acute pesticides poisonings in pregnant women. Przegl Lek 54(10):741-744.
151. DePeyster A, et al. 1993. Cholinesterase and self-reported pesticide exposure among pregnant women. Arch Env Health 48(5):348-352.
152. Longnecker MP, et al. 1999. Serial levels of serum organochlorines during pregnancy and postpartum. Arch Env Health 54(2):110-114.
153. Bush B, et al. 1984. Polychlorobiphenyl (PCB) congeners, p,p'-DDE, and hexachlorobenzene in maternal and fetal cord blood from mothers in upstate New York. Arch Env Contam Toxicol 13:517-527.
154. Ensslen SC, et al. 1990. [Demonstration of chlorinated hydrocarbons in follicular secretions]. Zentralbl Gynakol 112(19):1223-1226.
155. Levario-Carrillo M, et al. 2001. Parathion, a cholinesterase-inhibiting plaguicide induces changes in tertiary villi of placenta of women exposed. Gynecol Obstet Invest 52(4):269-275.
156. Rappolt RT, et al. 1968. Kern County: Annual generic pesticide input; blood dyscrasias; p,p'- DDE and p,p'-DDT residues in human fat, placentas with related stillbirths and abnormalities Ind Med Surg 37(7):513.
157. Arbuckle TE, et al. 1999. 2,4-dichlorophenoxyacetic acid residues in semen of Ontario farmers. Reprod Toxicol 13(6):421-429.
158. Stachel B, et al. 1989. Toxic environmental chemicals in human semen: analytical method and case studies. Andrologia. 21(3):282-291.
159. Kumar R, et al. 2000. Chlorinated pesticides and heavy metals in human semen. Int J Androl 23(3):145-149.
160. Szymczynski G, et al.1981. Content of chlorinated pesticides in human semen of a random population. Int J Androl 4(6):669-674.
161. Tsatsakis AM, et al. 1996. Experience with acute paraquat poisoning in Crete. Vet Hum Toxicol 38(2):113-117.
162. Tsatsakis AM, et al. 1996. Experiences with acute organophosphate poisonings in Crete. Vet Hum Toxicol 38(2):101-107.
163. Potashnik G, et al. 1987. Dibromochloropropane: an 8 year reevaluation of testicular function and reproductive performance. Fertil Steril 47:317-323.
164. Potashnik G, et al. 1979. Effect of dibromochloropropane in human testicular function. Israel J Med Sci 15:438-442.
165. Althoff H, et al. 1987. [Toxic environmental factors in sudden infant death (SIDS)]. Z Rechtsmed 98(2):103-110.
166. Kleemann WJ, et al. 1991. Heavy metals, chlorinated pesticides and polychlorinated biphenyls in sudden infant death syndrome (SIDS). Int J Legal Med 104(2):71-75.
167. Bosse U, et al. 1996. [Chlorinated carbohydrate content of fetal and pediatric organs and tissues]. Zentralbl Hyg Umweltmed 198(4):331-339.
168. Hosie S, et al. 2000. Is there a correlation between organochlorine compounds and undescended testes? Eur J Ped Surg 10(5):304-309.
169. Abbott DC, et al. 1968. Organochlorine pesticide residues in human fat in Great Britain. Br Med J 3(5611):146-149.
170. Foster W, et al. 2000. Detection of endocrine disrupting chemicals in samples of second trimester human amniotic fluid. J Clin Endocrinol Metab 85(8):2954-2957.
171. O'Leary JA, et al. 1970. Transplacental passage of pesticides. Am J Obstet Gyn 107:65-68.
172. Whitehall JS, et al. 2000. Fetal exposure to pollutants in Townsville, Australia, detected in meconium. Ped Res 47(4 pt 2):299A
173. Hong Z, et al. 2002. Meconium: a matrix reflecting potential fetal exposure to organochlorine pesticides and its metabolites. Ecotoxicol Environ Saf. 51(1):60-64.
174. Yamagishi T, et al. 1972. [On the organochlorine pesticide residues in mother's body and her fetus' body.] Tokyo-To Eisei-Kyoku Gakkai-Shi 50:44-45.
175. Enrique MO, et al. 2002. Prevalence of fetal exposure to environmental toxins as determined by meconium analysis. Neurotoxicology 23(3):329-339.
176. Whyatt RM, et al. 2001. Measurement of organophosphate metabolites in postpartum meconium as a potential biomarker of prenatal exposure: a validation study. Env Health Persp 109(4):417-420.

177. Rhainds M, et al. 1999. Lead, mercury, and organochlorine compound levels in cord blood in Quebec, Canada. Arch Env Health 54(1):40-47.
178. Dallaire F, et al. 2002. Temporal trends of organochlorine concentrations in umbilical cord blood of newborns from the lower north shore of the St. Lawrence river (Quebec, Canada). Env Health Persp 110(8):835-838.
179. Lackmann GM. 2002. Polychlorinated biphenyls and hexachlorobenzene in full-term neonates. Reference values updated. Biol Neonate 81(2):82-85.
180. Dorea JG, et al. 2001. Perinatal metabolism of dichlorodiphenyldichloro-ethylene in Nicaraguan mothers. Env Res 86(3):229-237.
181. Sala M, Ribas, et al. 2001. Levels of hexachlorobenzene and other organochlorine compounds in cord blood. Chemosphere 43(4-7):895-901.
182. McGready R, et al. 2001. Safety of the insect repellent N,N-diethyl-M-toluamide (Deet) in pregnancy. Am J Trop Med Hyg 65(4):285-289.
183. Jemaa Z, et al. 1985. Hexachlorobenzene in Tunisian mothers' milk, cord blood and foodstuffs. IARC Sci Pub 77:139-142.
184. DePeyster A, et al. 1994. Cholinesterase activity in pregnant women and newborns. J Toxicol Clin Toxicol 32(6):683-696.
185. O'Leary JA, et al. 1972. Correlation of prematurity and DDE levels in fetal whole blood. In: Davies JE, et al (eds) Epidemiology of DDT, Futura Publ.Co., Mount Kisco, New York, pp 55-56.
186. Davies JE, et al. 1967. Disturbances of metabolism in organophosphate poisoning. Indus Med Surg 36(1):57-62.
187. Korrick SA, et al. 2000. Measurement of PCBs, DDE, and hexachlorobenzene in cord blood from infants born in towns adjacent to a PCB-contaminated waste site. J Expo Anal Env Epid 10(6 Pt 2):743-754.
188. Cooper SP, et al. 2001. Prenatal exposure to pesticides: A feasibility study among migrant and seasonal farmworkers. Am J Ind Med 40(5):578-585.
189. Burse VW, et al. 2000. Utilization of umbilical cords to assess in utero exposure to persistent pesticides and polychlorinated biphenyls. J Expo Anal Env Epid 10(6 Pt 2):776-788.

Chapter 7
Pesticides and Chronic Neurological Effects (draft)

The brain and peripheral nervous system are directly affected by pesticides both as targets of action and deposition sites. All classes of pesticides can affect brain and neural tissue even if they do not cause observable acute effects. The pesticides that most directly affect the nervous system are the organophosphate and N-methyl carbamate insecticides, which are responsible for most acute poisonings (see Chapter 3).

In addition to acute poisoning, organophosphates can produce subacute, delayed and chronic neurological, neurobehavioural and psychiatric syndromes. Evidence for chronic neurological and psychiatric effects of OP compounds have come from case reports, clusters of neurological diseases and from studies of exposed workers and other populations.

Both high and low level chronic exposures can affect the peripheral nervous system by slowing of conduction velocity, and denervation and other electromyographic findings (Table 1). Vibrotactile sensitivity impairment , and posture abnormalities have also been reported (Table 2).

Chronic Neurological Effects Associated with Pesticide Exposure

Nerve Conduction Velocity	Slowing
Reaction Time	Slowing
Motor/visual speed tests	Slowing
Learning / memory tasks	Poorer performance
Vibrotactile Sensitivity	Impaired
Postural Sway	Abnormal
Electroencephalogram	Increased beta activity
Visual Evoked Potentials	Decreased amplitude
Muscle strength	Decreased

Central nervous system effects are assessed by batteries of neurobehavioral and neuropyschological tests, which include learning, memory, and mood among others (Tables 3-A and 3-B).

Electroencephalograms are not often done in pesticide exposure. An increase in beta activity slowing has been reported; most findings are of small changes or no associations (Table 4).

Psychological and neurological effects of pesticides may be subtle and difficult to demonstrate unless a comprehensive set of test are done. This is usually not the case because of time constrains, and an effort to develop a test battery that can be used through out the world, in both literate and non-literate populations, so diverse population can be comapred.

Chronic neurological sequelae have been reported after apparent full recovery from acute organophosphate poisoning.

Parkinson's Disease: The chronic disease most consistently associated with pesticides is Parkinson's disease. Parkinson's disease is one of the most common neurodegenerative disorders associated with aging. It is characterized by a loss of the neurotransmitterdopamine in the substancia nigra, in the part of the brain that controls movement. First described in 1871, the cause of the disease. is still unknown.

Parkinson's Disease Incidence / 100,000 Ferrara, Italy 1967-1987

Urban areas	3.11
Rural Areas	6.32
Agric. workers	20.6

Source: Reference 91

Laboratory studies show exposure to a wide variety of neurotoxic compounds, including pesticides, can deplete dopamine in the brain in a variety of animals.

The first studies to link pesticides with agricultural production were done in Canada, suggesting an association with living in rural areas and drinking well water. More recent studies confirm an association with pesticide exposure, both occupational and in the home (Table 6).

Organophosphate Induced Delayed Neuropathy (OPIDN)
In severe cases of poisoning by some organophosphate, after a delay period of apparent recovery, muscle weakness, ataxia, and paralysis develop. This condition called organophosphate induced delayed neuropathy (OPIDN) is characterized by axon degeneration and degeneration of myelin in the peripheral and central nervous systems. Mild cases may recover, but more severe cases show symptoms of an upper motor neuron lesion in the lower limbs. The condition is rare, and most cases are due to suicidal ingestion of concentrated formulations (Table 7).

Pesticides* Linked to OPIDN

Chlorpyrifos
Dichlorvos (DDVP)
Fenthion
Femnitrothion
Leptophos
Malathion
Methamidophos
Mipafox
Trichlorfon
Trichloronate
TOCP*

* Not a pesticide (see text)

The delayed neurotoxic action is not related cholinesterase inhibition, but to the binding (phosphorylation) of a specific enzyme in the nervous tissue called neurotoxic-esterase. The cause is still not known.

Ginger Jake: Tthe capacity to produce delayed neurotoxicity is widespread among OP esters. The first cases of OPIDN in the U.S. were seen during the prohibition era before organophosphate insecticides came on the market. Triorthocresylphosphate (TOCP), an industrial degreaser which causes demyelination and paralysis when ingested was used an adulterant in an alcoholic extract of Jamaican ginger. Thousands of people who drank 'Ginger Jake' during prohibition developed paresthesia of the feet and aching of the calves in about 12 days, followed two to three days later by ataxia, and paralysis. [1,2,3].

Other Neurological Diseases Possibly Associated with Pesticide Exposure

Amyotrophic Lateral Sclerosis
Eye Disorders
Guillain Barre Syndrome
Movement Disorders
Multiple System Atrophy
Psychiatric Disorders
Reflex Sympathetic Dystrophy

Other Disease: There are few epidemiological studies of pesticide exposure and other neurological diseases. A study in Canada found no association with Alzheimer's disease. There are case reports of pesticide exposure associated with amyotrophic lateral sclerosis, eye disorders, Guillain Barre syndrome, movement disorders, multiple system atrophy, reflex sympathetic dystrophy, and several reports of psychiatric disorders (see Table 5).

Table 1
Nerve Conduction Velocity - Occupational Exposure
(See Appendix F for explanation of table)

Bulgaria OP[a].sprayers - median[4]	Incr. ampl. sig
Peroneal velocity	Decreased
England sensory deficits, mainly small fibers[5]	
Egypt Zn phos EMG part. denerv. ant tibial[6]	35%
Part. denerv. flexor digiti minimi	6.7%
Egypt formulators, applicators- depression[7]	Increased
Finland dipehnyl paper mill EMG abnornalities[8]	Increased
France methyl bromide peripheral neuropathy[b] [9]	Case report
Germany PCP median, radial nerves [©] [10]	Normal range
Peroneal, sural nerves	Normal range
Germany agric pest 3 ys or more WHAT? [11]	Decreased
India agric. fenthion ERPs[d] - P3 amplitude[12]	No sig diff
India agric.fenthion[e] cond. velocity slowing[13]	p < 0.05
Median latency increased	p < 0.1
Peroneal latency increased	p < 0.05
F min.H reflex. latency increased	p < 0.01
India OP[a] factory perip. neuropathy[14]	Increase sig.
Japan ETO[d] neuropathy lower limbs [15]	Case report
Japan ethylene oxide polyneuropathy[f] [16]	Case report
Netherlands agric OP[a] sensory off season[17,18]	Decr. p=.04
Motor velocity off season	Decr. P=.04
Sensory during spray season	Decr. p <.01
Netherlands flower growers 20 y median motor[19]	-1.1 m/sec
Median sensory decrease	-1.4 m/sec
Sural sensorydecrease	-0.9 m/sec
Peroneal motor -1.2 -1.3 m/sec	Decrease
Sural, peroneal refractory period	Increased
Netherlands flower growers >10 y NCV[20]	Small dec.sig
Sri Lanka OP[a] sprayers sensory velocity	Decr. p =0.01
US exterminators NCV vs total population[21]	No sig diff.
US Hispanic farm workers low OP[a] exposure[22]	
Sural nerve latency/amplitude	No sig diff
Ulnar nerve conduction velocity	No sig diff
Ulnar neuromuscular junct. function	No sig. diff
US ethylene oxide subacute polyneuropathy[f] [23]	Case report
Bilat. foot-drop, EMG denerv. potentials	
US ethylene oxide hospital workesr NCV[24]	No sig. diff
US Arkansas 2,4-D, 2,4,5-T factory workers [25]	
NCV slowing 46% exposed vs 5% control	Sig. diff
Sural nerve mean slowing	~5.2 m/sec
Median motor nerve slowing	~1.9 m/sec
Yugoslavia ethylene oxide polyneuropathy legs[26]	Case report

a) Organophosphates. **(b**) In one patient, symptoms improved in five months. In the other, paresthesia still present 2 yrs later, and visual after-effects. **[c]** Pentachlorophenol. Exposure from carpets, moth killers, pesticide sprays, wood preservatives. **(d)** Event related potentials. **(e)** No clinical evidence neuropathy or muscle weakness. **(f)** Ethylene oxide sterilizing facility -reverse flow of an exhaust fan, a blocked air conditioner filter, lack of protective mask. **(e)** Confirmed by sural nerve biopsies. **(f)** Gradual and complete return of strength in the lower extremities occurred 4 to 7 months after removal from exposure
(g) Standard deviation.

Table 2
Vibrotactile Sensitivity (VTS) and Postural Sway

Chile methyl bromide applicators[27]			
Threshold prior to exposure	2..4 seconds		
Threshold post exposure	2..85 seconds		
England OP(a) sheep dippers VTS[b] [28]	Increased		
England OP[a] sheep dippers[29]	**Symp.**	**No symp.**	
Contls			
2 point discrimination hand mm	22	13	8
2 pt discriminationr foot mm	34	10	11
Mean calf circumference cm	35.0	36.3	38.6
Nicaragua methamidophos pois. VTS incr.[c] [30]	> 25 %		
South Africa OP[a] sprayers exposure[31]	Pos. assoc.		
US chlorpyrifos applicators VTS and tremor[56]	No assoc.		
Postural stability and TCP[e] levels	Assoc.		
US exterminators postural sway[21]	Worse sig.		
VTS threshold	No sig. diff		
US chlordane nonocc. abnormal balance[32]	7 of 9 cases		
US California OP poisoned not hosp. VTS[33]	Poor perform.		
Hospitalization OP pois	Worse		
US Cali. fumigators[f] methyl bromide VTS [34]	Worse sig.		
US New York OP[a] applicators VTS[35]	Increased		
Methyl bromide, sulfuryl fluor. appl. VTS	Increased		
US NY farmer pest appl VTS dominant hand[36]	Incr. p <.001		
Non-dominant hand	Incr. p <.04		

Table 3-A
Neurobehavioral and Psychometric Testing - Farmers and Farm Workers
(See Appendix F for explanation of table)

Farmers	
Belgium mild cognitive dysfunction[37]	
Cross sectional study	OR 1.47
Prospective study	OR 2.02
England OP exposed sheep farmers[38]	
Sustained attention poorer perf	Poorer sig.
Speed information processing poorer perf	Poorer sig.
Short-term memory and learning	No difference
Ecuador farmer members of cooperative[39]	
WHO NCTB[(a)] Visual-spatial	Most sensitive
Netherlands Flower growers pest use >10yrs[20]	
Attention, perceptual coding	Small diff. sig
South Africa farm/sprayers chronic OP expos.[31]	
WHO NCTB[(a)] Pursuit-Aiming	Small assoc
Santa Ana pegboard	Small assoc.
US male farmers heavy expos. OPs [40]	
Reaction time, dominant hand	Slower sig.
Agricultural Workers	
Chile men chronic methyl bromide exposure.[27]	
Dynamometry prior to exposure	51.4 kg
Post exposure 2-5 weeks	47.2 kg
Nothingham - neg.auto-percep prior	11.2
Post exposrue	13.6
Costa Rica poisoned banana workers[(b)] [41]	
Psychomotor, visuomotor skills perf.	Poorer
Language skills, affect performance	Poorer
Digit-Symbol test performance	Poorer sig.
Neuropsychiatric symptoms	Marked incr.
Expos. che inhibitors[c] prior 3 months	Poorest perf.
France vineyard workers pest. exp[(d)] [42]	
Neuropsychiatric test. Poorer perf.	OR $\geq$ 2
India agric. sprayers exposed fenthion (Misra 1994)	
Benton poorer performance	Sig.
Memory poorer performance	Sig
Lexand poorer performance	Sig
Passalong poorer performance	Sig
Poland ♀ greenhouse wrkrs OP exposure[43]	
WHO NCTB[(a)] Reaction times	Increased
Motor steadiness	Reduced
US Hispanic children agric vs nonagric[44]	No diff.
US Dieldrin occupational exposure[45]	
Psycholog. tests performance 5/58	Poorer
Psychomotor tests[(h)] 47 /58	Poorer p < 05
Cognitive tests performance	Poorer
US New York male pest applicators OPs [35]	
Electrophysiological abnormalities one	
US CaliforniaCholinesterase-inhibited subjects[(f)] [46]	
Serial digits better performance	Sig.
US Washington apple orchard OP applicators[47]	
Neuropsychiatric tests pre- vs post-season	No diff
Acute Pesticide Poisoning in the Past	
Germany post acute pyrethroid poisoning[48]	
Cerebro-organic dis.; sensomoto neuropathy	
Nicaragua farm workers 2 yr post hospitalization[49]	
WHO NCTB[(a)] performance 5/6 subtests[(e)]	Poorer
Motor steadiness/dexterity vs controls poorer	Poorer sig.
US chlorpyrifos poisoned pest control operators[21]	
Pegboard turning poorer peformance	Poorer sig..
2 of 6 neurobehavioral tests performance	Poorer sig.
5 of 5 mood scale tests performance	Poorer siig.
Postural sway performance	Poorer
US California severe OP poisoning group[33]	
Sustained visual attention performance	Poorer sig.
Mood scales performance	Poorer sig.
US former OP poisoned (Savage 1988)	
Memory, abstraction, mood	No sig diff
Halstead-Reitan cerebral damage/dysfxn	Abnormal
MMPI[(g)] distress items	Increased
PRAPFI[(h)] complaints of disability	Increased
Audiometry, vision tests	No sig diff

a) World Health Organization Neurobehavioral CoreTest Battery. **(b)** 81 workers treated for mild OP and CB poisoning not requiring hospitalization compared to 130 with symptoms who did not seek treatment . **[c]** Cholinesterase inhibitors, OPs and CBs **(d)** 528 directly mixing/spraying (mean 22 years), 173 indirectly treated plants, 216 never exposed. **(e)** Verbal/visual attention and memory, visuo-motor speed, sequencing, problem solving. **(f)** RBC Che activity $\leq$ 70% of baseline, or plasma che$\leq$ 60% . Reductions present without symptoms of poisoning. **(g)** Minnesota Multiphasic Personality Inventory. **(h)** Patient's and Relative's Assessment of Patient Functioning Inventories .

Table 3-B
Neurobehavioral and Psychometric Testing
Pest Control Operators and Factory Workers, and Non-occupational Exposure
(See Appendix F for explanation of table)

Pest Control Operators / Factory Workers	
Costa Rica DDT exposed malaria workers[50]	
Overall perform (mean)	20% decr.
Verbal attn, visuomotor. speed, seq	> difference
5 motor, senory, cognitive. tests, yrs expos.	Sig. diff
Increase neuropsyc/psychiatric symptoms	OR 3.98
India factory Memory, learning , vigilance [©] [51]	Poorer
US Chlorpyrifos applicators [52]	
Lanthony color vision and TCP[(a)] levels	Assoc.
Contrast sensitivity 1 test and TCP levels	Assoc.
Olfactory dysfunction, visual acuity	No assoc.
Manual dexterity, eye–hand coordination	No assoc.
US exterminators Pegboard turning poorer perf.[21]	Sig.
Smell, vision	No sig. diff.
Visual/motor skill	No sig. diff.
US FL sulfuryl fluoride fumigators Pattern Memory[53]	Worse sig.
Olfactory testing vs all fumigant exposed	Worse sig
Santa Ana dom. hand vsl fumigant exposed	Worse sig
US CA methyl bromide fumigators[(b)] 23 of 27 tests[54]	Worse sig.
Ccognitive test poorer performance	Sig.
US ETO[(d)]. hosp. workers neuropsych. tests[24]	No sig. diff
Non-occupational Exposure	
Germany females residential exposure WPC[(e)] [55]	
Paired-assoc. learning poorer performance	Sig.
Benton poorer performance	Sig.
Reading/naming speed. poorer performance	Sig.
PCP blood levels poorer performance	Sig.
India Bhopal MIC[(f)] victims[(g)] sev/mod exposure[56]	
Learning, motor precision poorer performance	p< 0.01
Disability score significant correlation	r = 0.68.
US chlordane exposure - residential[32]	
Reaction time poorer perf	Sig.
Digit symbol, poorer perf	Sig.
Trail-making poorer perf	Sig.
Verbal recall poorer perf	Sig.
Mood-state	No diff.
Long-term memory	No diff
US Case report methyl bromide poisoning[57]	
Concentration, learning , memory	Impaired

(a) 3,5,6-trichloropyridinol a metabolite of chlorpyrifos. **(b)**Soil and structural applicators of methyl bromide and sulfuryl fluoride (Vikane). **(c)**Quinalphos manufacturing workers. **(d)**Ethylene oxide, gas used to sterilize hospital/dental equipment. **(e)**Wood preservatives, pentachlorophenol (PCP), lindane, others. **(f)**Methylisocyanate, toxic chemical released in explosion at factory manufacturing carbaryl (Sevin) in December 1984. **(g)**15 severely, 14 moderately, 23 mildly affected; mean age 38.2 (15-65); 30 males. Neurological examination was normal.

Table 4
EEG and Visual Evoked Potentials (VEP)

Bulgaria VEP amplitude OP[(a)] sprayers[4]	Sig. Incr.
Egypt EEG abnormal zinc phos. appts[6]	17.4%
Finland diphenyl paper mill workers [8]	37.5%
Netherlands VEP bulb flower growers	No sig. diff
EEG fast (beta) activity	Increase
Netherlands EEG farmers spectral freq.	Changes
Netherlands EEG-β farmer >10 yrs[20]	Sig diff
US EEG ethylene oxide hosp. wrkrs[24]	No sig diff.
US EEG prior OP poisoning	No sig. diff.
US sleep EEG REM sabin[(b)] workers	Increase
β-activity temp/occip/ central li	increase
Background voltage	Decrease
Alpha activity	Decrease

(a) Organophosphate insecticides.
(b) Sarin is not a pesticide but a nerve gas. It's mode of action is the same as organophosphate insecticides but it is much more potent.

Table 5
Other Nervous System Effects
(See Appendix F for explanation of table)

Alzheimer disease	
Canada Quebec Pesticide exposure[(a)58]	No assoc.
Amyotrophic Lateral Sclerosis	
Italy Conjugal 30 months apart [59]	Case report
Pesticides levels artesian wells	Not signif.
US Michigan Dow 2,4-D worker deaths(b)[60]	OR 3.45
US Washington agricutural chemical expo[61]	OR 2.0
Men any amount of exposure	OR 2.4
Men high vs no exposure, trend p= 0.03	OR 2.8
Men low vs no exposure	OR 1.5 ns
Women low vs no exposure	OR 0.9 ns
Eye Disorders	
France retrobulbar ocular neuritis methamidophos[62]	Case report
France persistent visual problems methyl bromide[63]	Case report
US IA,NC farmers retinal dege. fungicide applicators[64]	OR 1.8
Cumulative days of fungicide use trend	p= 0.011
US TE cortical blindness carbofuran ingestion[65]	Case report
US California optic atrophy methyl bromide[66]	Case report
US CA. OP reentry pois. visual probs. 4 mons[67]	
Guillain Barre Syndrome	
Switzerland farm worker OP exposure[68]	Case report
India OP poisoning[69]	Case report
Paraguay children[70] possible OP exposure	30% cases
US Arizona 28 y farm worker merphos spill[71]	Case report
Movement Disorders	
France myoclonus methyl bromide poisoning[(c)72]	Case report
Israel isofenphos ingestion pyramidal findings[73]	Case report
Multiple System Atrophy	
US pesticides/environ. toxins [(d)74]	11% cases
US pesticide exposure.[75]	Sig incr.
Psychiatirc Disorders	
England OP exposed sheep farmers incr. vulner[42]	Increased
Spain suicide rate farmers agricultural area s[76]	Increased
US CO farmers pesticide illness - depression[77]	OR 5.87
US CA dicofol pois. cogn/emot probs. 18 mos[78]	12 yr male
US methyl bromide pois[(e)] psych. symp. weeks[79]	Case report
US 2 crop duster pilots OP psychiatric sequelae[80]	Case report
Reflex Symphathetic Dystrophy	
Turkey secondary neuropathy dimethoate poisoning[81]	Case report

(a) Based on residential histories, agriculture census (1971-1991) herbicide, insecticide spraying in the area. **(b)** All 3 worked in manufacture /formulation of 2,4-D (1947-49, 1950-51, 1968-86), for varying durations of time (1.3, 1.8, and 12.5 years). **[c]** Lived 5 years in a stuporous state. Brain at autopsy: necrosis inferior colliculi, gliosis upper brain stem reticular formation, changes in dentate and pontine nuclei. **(d)** 1 case heavy occupational exposure to malathion, diazinon and formaldehyde. **(e)** 4 farm workers removing plastic sheets from treated soil.

Table 6
Parkinson's Disease and Pesticide Exposure - Increased and Decreased Risk
(See Appendix F for explanation of table)

Increased Risk - Farming/Agriculture	
Canada BC orchard workers[82]	OR 3.69
Any pesticide exposure	OR 2.3
Paraquat - postural tremors	p = 0.01
China Taiwan paraquat, trend signifcant[83]	Increase
Exposed but not to paraquat	Decrease
China Hong Kong herbicide use[84]	Increase sig.
Denmark men and women[85]	SHR[(a)] 1.3
Germany pesticides[86]	Increase
India, OPs[(b)] akinetic-rigidity[87]	Case report
International studies farming[88]	OR 1.42
Pesticide exposure	OR 1.85
Israel field work pre-parkinsonism[89]	p< .0001
Italy farming occupation[90]	OR 7.7
Italy pesticide/herbicide exposure[91]	OR 1.14[#]
Italy maneb extrapyramidal disorder[[c] 92]	Case report
Italy, 10% diquat spill[(d)93]	Case report
Italy, Ferrara agricultural workers[94]	IR 20.6[(e)]
Spain Caceres[95]	Increase[*]
Sweden handling agric. pesticides[96]	OR 1.9[#]
Handling agric. insecticides	OR 2.2[#]
US pilot organophosphate poisoning[97]	Case report
US California mortality by residence[(f)98]	OR 1.65
US Hawaii plantation worker > 20 yrs[99]	RR 1.9[*]
Pesticide exposed vs nonexposed	Increase[#]
US Iowa, North Carolina farm wives[100]	SMR 2.7[#]
US Michigan agricultural work[101]	OR 1.74[#]
Herbicide exposure[102]	OR 4.1
Insecticide exposure	OR 3.6
Farming occupation	OR 2.8
US National pesticide exposure[78]	OR 2.16
Farming occupation	OR 1.72
US Washington orchard workers[103]	PR 2.0[*]
Farming	No assoc.
US Washington farm job[104]	OR 3.2[#]
Increased Risk - Other Pesticide Exposure	
Brazil glyphosate accident[(g)105]	Case report
Germany wood preservatives[76]	Increase
Israel urban population exposed to pest.[106]	Increase
Sweden handling pest. any occupation	OR 2.8[#]
US Kansas occupational herbicides[107]	Increase
US Washington onset age les than 50[108]	
Insecticide exposure	OR 5.75
Herbicide exposure	OR 3.22
Residence fumigated house	OR 5.25
Increased Risk - Rural Living	
Australia[109]	OR 1.8
Canada raised in a rural area[110]	Increase
China, Hong Kong[74]	Increase
Finland[111]	No assoc.
International meta-analysis[78]	OR 1.56
US blacks [112]	Increase
US Kansas[113]	Increase
US National meta-analysis[78]	OR 2.17
US Washington State onset < age 50[98]	OR 2.72
Increased Risk - Well Water Use	
China, Taiwan onset age < 40[114]	OR 10.92
Spring water	OR 10.57
India for more than 10 years[115]	Increase
International studies meta-analysis[78]	OR 1.26[*]
Italy (on a farm)[9]	OR 2.0
Italy[10]	OR 2.8
Spain Madrid for 30 yrs or more[116]	Increase
US Kansas[32]	Increase
US meta-analysis[7]	OR 1.44[*]
U.S. drinking unfiltered water[102]	Increase
Decreased Risk - Farming/Agriculture	
Canada Quebec farm work[117]	No assoc
Finland pesticide/herbicides[30]	No assoc.
International studies meta-analysis[118]	No assoc.
Italy Sicily[119]	OR 0.6
Spain Caceres[85]	No assoc.
US Kansas[97]	No assoc.
US Washington[22]FIXX	No assoc.
US Hispanics[31] FIXX	Decrease
Decreased Risk - Other Pesticide Exposure	
Australia pesticides/herbicides[99]	No assoc.
Canada Que. pesticides/herbicides[107]	No assoc.
Spain, Madrid past exposure[106]	No assoc.
US sibling pairs[120]	No assoc.
US New England[121]	No assoc.
US Kansas[97]	No assoc.
US onset < age 40 and > age 60[122]	No assoc.
US Washington home use[98]	No trends
Decreased Risk - Rural Living	
Canada, Calgary[123]	No assoc.
Canada Quebec[107]	OR 0.31
Germany rural factors[76]	No assoc.
US < age 40 and > age 60[112]	No assoc.
Decreased Risk - Well Water Use	
Australia[99]	Decrease
Canada, Calgary[113]	No assoc.
Canada Quebec[36]	No assoc.
Finland[101]	No assoc.
US New England[111]	Decrease
US Washington State[93]CHECK	No assoc.
US < age 40 and > age 60[112]	No assoc.

* Borderline significance # Not significant

(**a** Standardized Hospitalization Ratio **(b**) Organophosphates. 4 recovered, 1 repeat on re-exposure. **[c**] 37 yr old man, 2 years between exposure and onset. **(d**) 72 yr farmer. CT, MRI abnormal. Persisted 4 mon. later.**(e**)Incidence/100,000. IR in urban areas 3.1, in rural areas 6.32.**(f)** 1982 data, when all use was not reported.**(g**) Parkinsonian syndrome 1 month after, MRI changes 2 yrs later

Table 7
Organophosphate Induced Delayed Neuropathy

Australia chlorpyrifos termite applicators[124]	
Mean NTE [(a)] activity	Slightly higher
Mean serum Che compared to controls	52% reduction
Belgium fenthion ingestion 65 yr female[125]	Case report
7 days post-exposure distal axonopathy	
Brazil trichlorfon poisoning farm worker[126]	Case report
3 mon later distal predom motor neuropathy	
EMG denervation changes	
NCV reduced sensory and motor	
Sural nerve biopsy axonal degeneration	
China methamidophos poisoning OPIDN[127]	13.5% cases
All recovered 1½ yrs wo perm. disability	
China, Taiwan complication mevinphos pancreatitis[128]	Case report
China, Taiwan carbofuran 23 m suicide[129]	Case report
EMG sensorimotor neuropathy	
4 months to recovery .	
England research chemist - Mipafox[130]	Case report
England 2-8 wks post trichlorfon poisoning[131]	Case report
France farm workers mod. pois. methamidophos[65]	Case report
Sensory and motor peripheral neuropathy	
Full recovery after 18th months	
Germany physotol 39-year-old woman farmer[132]	Case report
Severe polyneuropathy	
NTE inhibition	
Greece attempted suicide mecarbam[133]	Case report
Polyneuropathy	
Greece, Crete 1/6 poisoning[134]	Case report
Hungary trichlorfon 2 suicide attempts[135]	Case report
Polyneuropathy 2 wks after apparent recovery	
Hypesthesia, paresthesia, paresis peroneal	
EMG severe axon degen. primarily motor	
Biopsy revealed demyelination	
Recovered 18 months, residual peroneal paresis	
India bilateral recurrent laryngeal nerve palsy[136]	Case report
Italy suicide attempt chlorpyrifos ingestion[137]	Case report
30 d later lymphocytic NTE 60% inhibited	
43rd d paresthesia and leg weakness	
EMG, biopsy axonal polyneuropathy	
Italy 2 cases 1 chlorpyrifos poisoning[138]	Case report
Japan 1st report of malathion OPIDN (in alcoholic)[139]	Case report
7th hosp d glove/stocking flaccid quadriplegia	
2 months neurogenic bladder, spinal automatism	
7 months, spasticity lower limbs.	
Sural biopsy axonal degen., Schwann cell clusters	
Nicaragua methamidophos, chlorpyrifos pois[140]	
Hand grip 7 wks post poisoning	Imaired
Pinch strength 7 wks post poisoning	impaired
In intentional poisonings impairment	More severe
2 year follow-up hand strength impairment[141]	Persistent
Suicidals worse second examination	
Deficits not related to pesticide type	
Poland suicide attempt trichloronate[142]	Case report
Romania 4 accidental ingestion trichlorfon[143]	Case reports
3-5 wks distal predom. motor neuropathy	
Distal weakness, foot drop, hypotonia.	
Ankle jerk lost, other DTRs normal	
2 mon. later knee jerks brisk, patellar clonus	
Loss abdom. cutaneous reflexes, Babinski sign	
EMG- dying-back neuropathy	
Spain farm worker expos. age 14-24[144]	Case report
EMC predom. motor axonal polyneuropathy	
Nerve biopsy 'dying back' axonopathy	
Sri Lanka 3 suicide attempts[145]	Case report
25-35 d after bilateral vocal cord paralysis	
Sri Lanka methamidophos agric sprayers[146]	33%
Turkey suicide attempts trichlorfon, fenthion[147]	Case reports
Turkey of 32 cases 21.8% intermed. syndrome[148]	
US child chlorpyrifos ingestion vocal cord paralysis[149]	
US carbaryl ingestion[150]	Case report
Acute weakness of arms and legs	
EMG axonal peripheral neuropathy	
Recovery continued for 9 months	
US workers DEF, merphos[151]	
Lymphocyte NTE aerial/grnd applicatorss	No effects
US 16-y boy methamidophos[152]	Case report
Day 3 lymphocyte NTE 77% decr. activity	
2 wks neuropathy profound LE weakness	
Decr. ulnar, absent tibial action potentials	
NCVs normal	
Serum IgG neural antibodies increased	
US Velsicol leptohpos workers[153]	
12 workers serious neurological disorders, 2 milder	
63/155 abnormalities one or more objective tests	
11/63 abnormal nerve function, psychological tests	
US Texas 12 leptophos workers[154]	

(a) Neuropathy target esterase.

References

1. Metcalf RL. 1982. Historical perspective of organophosphorus ester-induced delayed neurotoxicity Neurotoxicology 3(4):269-284.
2. Morgan JP, et al. 1978. Jamaica ginger paralysis. Forty-seven year follow-up. Arch Neurol 35(8): 530-532.
3. Shea KP. 1974. Nerve damage 1974. the return of "ginger jake"? Environment 16:6-9.
4. Datsov E. 1990. [An electroneurographic study of agricultural workers working with organophosphate pesticides]. Probl Khig 15:55-61
5. Jamal GA, et al. 2002.A clinical neurological, neurophysiological, and neuropsychological study of sheep farmers and dippers exposed to organophosphate pesticides. Occ Env Med 59(7):434-441.
6. Amr MM, et al. 1997. Neuropsychiatric syndromes and occupational exposure to zinc phosphide in Egypt. Env Res 73(1-2):200-206.
7. Amr MM, et al. 1997. Psychiatric disorders among Egyptian pesticide applicators and formulators. Env Res 73(1-2):193-199.

8. Seppalainen AM, et al. 1975. Electrophysiological findings in diphenyl poisoning. J Neurol Neurosurg Psychiatry 38(3):248-52.
9. DeHaro L, et al. 1997. Central and peripheral neurotoxic effects of chronic methyl bromide intoxication. J Toxicol Clin Toxicol 1997;35(1):29-34
10. Triebig G, et al. 1987. Pentachlorophenol and the peripheral nervous system: a longitudinal study in exposed workers. Br J Ind Med 44:638-641.
11. Roder H, et al. 1976. [Electroneurographical examination of agricultural workers exposed to plant protective agents]. Psychiatr Neurol Med Psychol (Leipz) 28(10):630-634.
12. Misra UK, et al. 1994. A study of cognitive functions and event related potentials following organophosphate exposure. Electromyogr Clin Neurophysiol 34(4):197-203.
13. Misra UK, et al. 1988. A study of nerve conduction velocity, late responses and neuromuscular synapse functions in organophosphate workers in India. Arch Toxicol 61(6):496-500
14. Engel LS, et al. 1998. Neurophysiological function in farm workers exposed to organophosphate pesticides. Arch Env Health 53(1):7-14.
15. Fukushima T, et al. 1986. Chronic ethylene oxide poisoning in a factory manufacturing medical appliances. J Soc Occup Med 36(4):118-123.
16. Kuzuhara S, et al. 1983. Ethylene oxide polyneuropathy. Neurology 33:377-380.
17. Peiris-John RJ, et al. 2002. Effects of occupational exposure to organophosphate pesticides on nerve and neuromuscular function. J Occ Env Med 44(4):352-357.
18. Peiris-John RJ, et al. 2002. Effects of occupational exposure to organophosphate pesticides on nerve and neuromuscular function. J Occ Env Med 44(4):352-357.
19. Ruijten MW, et al. 1994. Effect of chronic mixed pesticide exposure on peripheral and autonomic nerve function. Arch Env Health 49(3):188-195.
20. Verberk MM, et al. 1990. Health effects of pesticides in the flower-bulb culture in Holland. Medicina del Lavoro 81(6):530-541.
21. Steenland K, et al. 2000. Neurologic function among termiticide applicators exposed to chlorpyrifos. Env Health Persp 108(4):293-300.
22. Engel LS, et al. 1998. Neurophysiological function in farm workers exposed to organophosphate pesticides. Arch Env Health 53(1):7-14.
23. Finelli PF, et al. 1993. Ethylene oxide-induced polyneuropathy. A clinical and electro-physiologic study. Arch Neurol 40(7):419-421.
24. Estrin WJ, et al. 1990. Neurotoxicological evaluation of hospital sterilizer workers exposed to ethylene oxide. Clin Toxicol 28(1):1-20.
25. Singer R, et al. 1982. Nerve conduction velocity of workers employed in the manufacture of phenoxy herbicides. Env Res 29:297-311.
26. Kovac S, et al. 1984. Ethylene oxide-induced polyneuropathy. Arhiv za Higijenu Rada i Toksikologiju 35(1):3-10.
27. Acuna MC, et al. 1997. [Assessment of neurotoxic effects of methyl bromide in exposed workers]. Rev Med Chil 125(1):36-42.
28. Pilkington A, Buchanan D, Jamal GA, et al. 2001. An epidemiological study of the relations between exposure to organophosphate pesticides and indices of chronic peripheral neuropathy and neuropsychological abnormalities in sheep farmers and dippers. Occ Env Med 58(11):702-710.
29. Beach JR, Spurgeon A, Stephens R, et al. 1996. Abnormalities on neurological examination among sheep farmers exposed to organophosphorous pesticides. Occup Env Med 53:520-525.
30. McConnell R, Keifer M, Rosenstock L. 1994. Elevated quantitative vibrotactile threshold among workers previously poisoned with methamidophos and other organophosphate pesticides. Am J Ind Med 25(3):325-334.
31. London L, Myers JE, Nell V, et al. 1997. An investigation into neurologic and neurobehavioral effects of long- term agrichemical use among deciduous fruit farm workers in the Western Cape, South Africa. Env Res 73(1/2):132-145.
32. Kilburn KH, Thornton JC. 1995. Protracted neurotoxicity from chlordane sprayed to kill termites. Env Health Persp 103(7-8):690-694.
33. Steenland K, Jenkins B, Ames RG, et al. 1994. Chronic neurological sequelae to organophosphate pesticide poisoning. Am J Pub Health 84(5):731-736.
34. Anger WK, Moody L, Burg J, et al. 1986. Neurobehavioral evaluation of soil and structural fumigators using methyl bromide and sulfuryl fluoride. Neurotoxicology 7(3):137-156.
35. Horowitz SH, Stark A, Marshall E, et al. 1999. A multi-modality assessment of peripheral nerve function in organophosphate-pesticide applicators. J Occ Env Med 41(5):405-408.
36. Stokes L, Stark A, Marshall E, et al. 1995. Neurotoxicity among pesticide applicators exposed to organophosphates. Occ Env Med 52(10):648-653.
37. Bosma H, et al. 2000. Pesticide exposure and risk of mild cognitive dysfunction. Lancet 356(9233):912-913.
38. Stephens R, et al. 1995. Neuropsychological effects of long-term exposure to organophosphates in sheep dip. Lancet 345(8958):1135-1139
39. Cole DC, et al. 1997. Neurobehavioral outcomes among farm and nonfarm rural Ecuadorians. Neurotoxicol Teratol 19(4):277-286.
40. Fiedler N, et al. 1997. Long-term use of organophosphates and neuropsychological performance. Am J Ind Med 32(5):487-496.
41. Wesseling C, et al. 2002. Long-term neurobehavioral effects of mild poisonings with organophosphate and n-methyl carbamate pesticides among banana workers. Int J Occ Env Health 8(1):27-34.
42. Baldi I, et al. 2001. Neuropsychologic effects of long-term exposure to pesticides: results from the French Phytoner study. Env Health Persp 109(8):839-844.
43. Bazylewicz-W B, et al. 1999. Behavioral effects of occupational exposure to organophosphorous pesticides in female greenhouse planting workers. Neurotoxicol 20(5):819-826.
44. Rohlman DS, et al. 2001. Assessment of neurobehavioral function with computerized tests in a population of Hispanic adolescents working in agriculture. Env Res. 85(1):14-24.
45. Sandifer SH, et al. 1981. A case-control study of persons with elevated blood levels of dieldrin. Arch Env Contam Toxicol 10:35-45.
46. Ames RG, et al. 1995. Chronic neurologic sequelae to cholinesterase inhibition among agricultural pesticide applicators. Arch Env Health 50(6):440-444.
47. Daniell W, et al. 1992. Neuropsychological performance among agricultural pesticide applicators. Env Res 59(1):217-228.
48. Muller-Mohnssen H. 1999. Chronic sequelae and irreversible injuries following acute pyrethroid intoxication. Toxicol Lett 107(1-3):161-176.
49. Rosenstock L, et al. 1990. Chronic neuropsychological sequelae of occupational exposure to organophosphate insecticides. Am J Indus Med 18:321-325.
50. VanWendelDeJoode B, et al. 2001 Chronic nervous-system effects of long-term occupational exposure to DDT. Lancet 357(9261):1012-1015.
51. Srivastava AK, et al. 2000. Clinical, biochemical and neurobehavioural studies of workers engaged in the manufacture of quinalphos. Food Chem Toxicol 38(1):65-69.
52. Dick RB, et al. 2001. Evaluation of acute sensory--motor effects and test sensitivity using termiticide workers exposed to chlorpyrifos. Neurotoxicol Teratol 23(4):381-93.
53. Calvert GM, Mueller CA, Fajen JM, et al. 1998. Health effects associated with sulfuryl fluoride and methyl bromide exposure among structural fumigation workers. Am J Public Health 88(12):1774-1780.
54. Anger WK, et al. 1986. Neurobehavioral evaluation of soil and structural fumigators using methyl bromide and sulfuryl fluoride. Neurotoxicology 7(3):137-156.
55. Peper M,. 1999. Long-term exposure to wood-preserving chemicals containing pentachlorophenol and lindane is related to neurobehavioral performance in women. Am J Ind Med 35(6):632-641.

56. Misra UK, et al. 1987. A study of cognitive functions in methylisocyanate victims one year after Bhopal accident. Neurotoxicology 18(2):381-386.
57. Reidy TJ, et al. 1994. Neuropsychological sequelae of methyl bromide: a case study. Brain Injury 8(1):83-93.
58. Gauthier E, et al. 2001. Environmental pesticide exposure as a risk factor for Alzheimer's disease: a case-control study. Env Res 86(1):37-45.
59. Poloni M, et al. 1997. Conjugal amyotrophic lateral sclerosis: toxic clustering or change? Ital J Neurol Sci 18(2):109-112.
60. Burns CJ, et al. 2001. Mortality in chemical workers potentially exposed to 2,4-D 1945-94: an update. Occ Env Med 58(1):24-30.
61. McGuire V, et al. 1997. Occupational exposures and amyotrophic lateral sclerosis. A population-based case-control study. Am J Epid 145(12):1076-1088.
62. DeHaro L, et al. 1999.[Methamidophos intoxication: immediate and late neurological toxicity; two case reports]. Acta Clin Belg Suppl 1:64-67.
63. DeHaro L, et al. 1997. Central and peripheral neurotoxic effects of chronic methyl bromide intoxication. J Toxicol Clin Toxicol 35(1):29-34.
64. Kamel F, et al. 2000. Retinal degeneration in licensed pesticide applicators. Am J Ind Med 37(6):618-628.
65. Baban NK, et al. 1998. Human sequelae of severe carbamate poisoning. Tenn Med 91(3):103-106.
66. Chavez CT, et al. 1985. Methyl bromide optic atrophy. Am J Ophthalmol 99(6):715-719.
67. Whorton MD, et al.1983. Persistence of symptoms after mild to moderate acute organophosphate poisoning among 19 farm field workers. J Toxicol Env Health 11(3):347-354.
68. Breaud P, et al. 1979. [A case of acute toxic polyneuropathy in a young agricultural worker]. Rev Med Suisse Romande 99(3):149-154.
69. Adlakha A, et al. 1987. Guillain Barre syndrome as a sequela of organophosphorus poisoning. J Assoc Physicians India 35(9):665-666.
70. Hart DE, et al. 1994. Childhood Guillain-Barre syndrome in Paraguay, 1990 to 1991. Ann Neurol 36(6):859-863.
71. Fisher JR. 1977. Guillain-Barre syndrome following organophosphate poisoning. JAMA 238:1950-1951.
72. Goulon M, et al. 1975. [Methyl bromide poisoning. 3 cases, 1 fatal. Neruopathological study of one case of coma with myoclonus followed for 5 years]. Rev Neurol 131(7):445-468.
73. Catz A, et al. 1988. Late onset isofenphos neurotoxicity. J Neurol Neurosurg Psychiatry 51(10):133813-40.
74. Hanna PA, et al. 1999. Multiple system atrophy: the putative causative role of environmental toxins. Arch Neurol 56(1):90-94.
75. Nee LE, et al. 1991. Environmental-occupational risk factors and familial associations in multiple system atrophy. Clin Auton 1(1):9-13.
76. Parron T, et al. 1996. Increased risk of suicide with exposure to pesticides in an intensive agricultural area. A 12-year retrospective study. Forensic Sci Int 79(1):53-63.
77. Stallones L, et al.. 2002. Pesticide poisoning and depressive symptoms among farm residents. Ann Epid 12(6):389-394.
78. Lessenger JE, et al. 1991. Neurotoxicities and behavioral changes in a 12-year-old male exposed to dicofol, an organochloride pesticide. J Toxicol Env Health 33(3):255-261.
79. Herzstein J, et al. 1990. Methyl bromide intoxication in four field-workers during removal of soil fumigation sheets. Am J Ind Med 17:321-326.
80. Dille JR, et al. 1964. Central nervous system effects of chronic exposure to organophosphate insecticides. Aerospace Med 35:475-78.
81. Sahin M, et al. 1994. Reflex sympathetic dystrophy syndrome secondary to organophosphate intoxication induced neuropathy. Ann Nucl Med 8(4):299-300.
82. Kelly SJ, et al. 1994. Parkinson's Disease: two case control studies of occupational and environmental risk factors. In: McDuffie HH, et al (eds) Agricultural Health and Safety. Univ. Saskatchewan, Canada.
83. Liou HH, et al. 1997. Environmental risk factors and Parkinson's disease: a case-control study in Taiwan. Neurology 48(6):1583-1588.
84. Ho SC, et al. 1989. Epidemiologic study of Parkinson's disease in Hong Kong. Neurology. 39(10):1314-1318.
85. Tuchsen F, et al. 2000. Agricultural work and the risk of Parkinson's disease in Denmark, 1981-1993. Scand J Work Env Health 26(4):359-362.
86. Seidler A, et al. 1996. Possible environmental, occupational, and other etiologic factors for Parkinson's disease. Neurology 46(5):1275-1284.
87. Bhatt MH, et al. 1999. Acute and reversible parkinsonism due to organophosphate pesticide intoxication: five cases. Neurology 52(7):1467-1471.
88. Priyadarshi A, et al. 2001. Environmental risk factors and Parkinson's disease: a meta-analysis. Env Res 86(2):122-127.
89. Herishanu YO, et al. 1998. A case-referent study of extrapyramidal signs (preparkinsonism) in rural communities of Israel. Can J Neurol Sci 25(2):127-133.
90. Zorzon M, et al. 2002. Familial and environmental risk factors in Parkinson's disease. Acta Neurol Scand 105(2):77-82.
91. Smargiassi A, et al. 1998. A case-control study of occupational and environmental risk factors for Parkinson's disease in the Emilia-Romagna region of Italy. Neurotoxicology 19(4-5):709-712.
92. Meco G, et al. 1994. Parkinsonism after chronic exposure to the fungicide maneb (manganese ethylene-bis-dithiocarbamate). Scand J Work Env Health 20:301-305.
93. Sechi GP, et al. 1992. Acute and persistent Parkinsonism after use of diquat. Neurology 42:261-263.
94. Granieri E, et al. 1991. Parkinson's disease in Ferrara, Italy, 1967 through 1987. Arch Neurol 48(8):854-857.
95. Morano A, et al. 1994. Risk-factors for Parkinson's disease: case-control study in the province of Caceres, Spain. Acta Neurol Scand 89(3):164-710.
96. Fall PA, et al. 1999. Nutritional and occupational factors influencing the risk of Parkinson's disease. Mov Disord 14(1):28-37.
97. Davis KL, et al. 1978. Possible organophosphate-induced Parkinsonism. J Nerv Men Dis 166:222-225.
98. Ritz B, et al. 2000. Parkinson's disease mortality and pesticide exposure in California 1984-1994. Int J Epid 29(2):323-329.
99. Petrovitch H, et al. 2002. Plantation work and risk of Parkinson disease in a population-based longitudinal study. Arch Neurol 59:1787-1792.
100. Blair A, et al. 2002. Mortality among farmers and spouses in the agricultural health study. Ann Epid 12(7):507.
101. Kirkey KL, et al. 2001. Occupational categories at risk for Parkinson's disease. Am J Ind Med 39(6):564-571.
102. Gorell JM, et al. 1998. The risk of Parkinson's disease with exposure to pesticides, farming, well water, and rural living. Neurology 50(5):1346-1350.
103. Engel LS, et al. 2001. Parkinsonism and occupational exposure to pesticides. Occ Env Med 58:582-589.
104. Wechsler LS, et al. 1991. A pilot study of occupational and environmental risk factors for Parkinson's disease. Neurotoxicology 12(3):387-392.
105. Barbosa ER, et al. 2001. Parkinsonism after glycine-derivate exposure. Mov Disord 16(3):565-568.
106. Herishanu YO, et al. 2001. A case-control study of Parkinson's disease in urban population of southern Israel. Can J Neurol Sci 28(2):144-147.
107. Hubble JP, et al. 1992. Herbicide-pesticide exposure independent of rural living as a risk factor for Parkinson's disease. Neurology 42 (4 Suppl 3):174.
108. Butterfield PG, et al. 1993. Environmental antecedents of young-onset Parkinson's disease. Neurology 43(6):1150-1158.
109. McCann SJ, et al. 1998. The epidemiology of Parkinson's disease in an Australian population. Neuroepidemiology 17(6):310-317.
110. Rajput AH, et al. 1987. Geography, drinking water chemistry, pesticides and herbicides and the etiology of Parkinson's disease. Can J Neurolog Sci 14:414-418.
111. Kuopio AM, et al. 1999. Environmental risk factors in Parkinson's disease. Mov Disord 14(6):928-939.
112. Marder K, et al. 1998. Environmental risk factors for Parkinson's disease in an urban multiethnic community. Neurology 50(1):279-281.
113. Koller W, et al. 1990. Environmental risk factors in Parkinson's disease. Neurology 40(8):1218-1221.
114. Tsai CH, et al. 2002. Environmental risk factors of young onset Parkinson's disease: a case-control study. Clin Neurol Neurosurg 104(4):328-333.

115. Behari M, et al. 2001. Risk factors of Parkinson's disease in Indian patients. J Neurol Sci 190(1-2):49-55.
116. Jimenez-J FJ, et al. 1992. Exposure to well water and pesticides in Parkinson's disease: a case-control study in the Madrid area. Mov Disord 7(2):149-152.
117. Zayed J, et al. 1990. [Environmental factors in the etiology of Parkinson's disease]. Can J Neurol Sci 17(3):286-291.
118. Priyadarshi A, et al. 2000. A meta-analysis of Parkinson's disease and exposure to pesticides. Neurotoxicology 21(4):435-440.
119. Rocca WA, et al. 1996. Occupation, education, and Parkinson's disease: a case-control study in an Italian population. Mov Disord 11(2):201-206.
120. Maher NE, et al. 2002. Epidemiologic study of 203 sibling pairs with Parkinson's disease: The GenePD study. Neurology 58(1):79-84.
121. Taylor CA, et al. 1999. Environmental, medical, and family history risk factors for Parkinson's disease. Am J Med Genet 88(6):742-749.
122. Stern M, et al. 1991. The epidemiology of Parkinson's disease. A case-control study of young-onset and old-onset patients. Arch Neurol 48(9):903-907.
123. Semchuk KM, et al. 1991. Parkinson's disease and exposure to rural environmental factors: a population based case-control study. Can J Neurol Sci 18(3):279-286.
124. Dyer SM, et al. 2001. Peripheral cholinesterase inhibition by occupational chlorpyrifos exposure in Australian termiticide applicators. Toxicology 169(3):177-185.
125. VandenNeucker K, et al. 1991. The neurophysiologic examination in organophosphate ester poisoning. Electromyogr Clin Neurophysiol 31(8):507-511.
126. DeFreitas MR, et al. 1990. [Polyneuropathy caused by trichlorfon]. Arq Neuropsiquiatr 48(4):515-519.
127. Sun DH, et al. 1998. Epidemiologic survey on organophosphate-induced delayed polyneuropathy (OPIDP) among patients recovered from methamidophos poisoning. Med Lav 89(Suppl 2):S123-128.
128. Hsiao CT, et al. 1996. Acute pancreatitis following organophosphate intoxication. J Toxicol Clin Toxicol 34(3):343-347.
129. Yang PY, et al. 2000. Carbofuran-induced delayed neuropathy. J Toxicol Clin Toxicol 38(1):43-46.
130. Bidstrup PL. 1989. Perspective on safety: personal opinions (1989 Yant Memorial Award lecture). Am Ind Hyg Assoc J 50(10):505-509.
131. Hierons R, et al. 1978. Clinical and toxicological investigations of a case of delayed neuropathy in man after acute poisoning by an organophosphorus pesticide. Arch Toxicol 40:279-284.
132. Lahman B, et al. 1990. Severe polyneuropathy as a result of organophosphate poisoning. Med Pr 41(5):360-362.
133. Stamboulis E, et al. 1991. Neuropathy following acute intoxication with Mecarbam (OP ester). Acta Neurol Scand 83(3):198-200.
134. Tsatsakis AM, et al. 1996. Experiences with acute organophosphate poisonings in Crete. Vet Hum Toxicol 38(2):101-107.
135. Iranyi J. 1975. Organophosphate-induced polyneuropathy. Orv. Hetil 116(27):1572-1575.
136. Vaidya SR, et al. 2002. Life threatening stridor due to bilateral recurrent laryngeal nerve palsy as an isolated manifestation of intermediate syndrome. J Assoc Physicians India 50:454-455. [No
137. Lotti M, et al. 1986. Inhibition of lymphocytic neuropathy target esterase predicts the development of organophosphate-induced delayed polyneuropathy. Arch Toxicol 59(3):176-179.
138. Moretto A, et al. 1998. Poisoning by organophosphorus insecticides and sensory neuropathy. J Neurol Neurosurg Psychiatry 64(4):463-468.
139. Komori T, et al. 1991. A case of delayed myeloneuropathy due to malathion intoxication. Brain Nerve (Tokyo) 43(10):969-974.
140. Miranda J, et al. 2002. Onset of grip- and pinch-strength impairment after acute poisonings with organophosphate insecticides. Int J Occ Env Health 8(1):19-26.
141. Miranda J, et al. 2004. Muscular strength and vibration thresholds during two years after acute poisoning with organophosphate insecticides. Occ Env Med 61(1):e4.
142. Jedrzejowska H, et al. 1980. Neuropathy due to phytosol (Agritox). Report of a case. Acta Neuropathol. 49(2): 163-168.
143. Vasilescu C, et al. 1984. Delayed neuropathy after organophosphorus insecticide (Dipterex) poisoning. J Neurol Neurosurg Psychiatry 47(5):543-548.
144. Carod-Artal FJ, et al. 1999. [Late onset polyneuropathy due to exposure to organophosphates]. [Spanish]. Rev Neurol 29(2):123-127.
145. DeSilva HJ, et al. 1994. Isolated bilateral recurrent laryngeal nerve paralysis: a delayed complication of organophosphorus poisoning. Hum Exper Toxicol 13(3):171-173.
146. Senanayake N, et al. 1982. Acute polyneuropathy after poisoning by a new organophosphate insecticide. N Eng J Med 306(3):155-157.
147. Karademir M, et al. 1990. Two cases of organophosphate poisoning with development of intermediate syndrome. Hum Exp Toxicol 9(3):187-190.
148. Aygun D, et al. 2002. Serum acetylcholinesterase and prognosis of acute organophosphate poisoning. J Toxicol Clin Toxicol 40(7):903-910.
149. Aiuto LA, et al. 1993. Life-threatening organophosphate-induced delayed polyneuropathy in a child after accidental chlorpyrifos ingestion. J Ped 122(4):658-660.
150. Dickoff DJ, et al. 1986. Delayed neurotoxicity after ingestion of carbamate pesticide. Neurology 37(7):1229-1231.
151. Lotti M, et al. 1983. Occupational exposure to the cotton defoliants DEF and merphos. J Occ Med 25:517-522.
152. McConnell R, et al. 1999. Organophosphate neuropathy due to methamidophos: biochemical and neurophysiological markers. Arch Toxicol 73(6):296-300.
153. NIOSH. 1977. Testimony on Velsicol Chemical Co., Leptophos, by B. F. Craft, Dec.13, 1977.
154. Xintaras C, et al. 1979. Neurotoxic effects of exposed chemical workers. Ann NY Acad Sci 329:30-38.