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THE USE OF SINGLE PHOTON EMISSION COMPUTED TOMOGRAPHY TO INDICATE NEUROTOXICITY IN CASES OF PESTICIDE AND SOLVENT EXPOSURES

DISSERTATION

Presented to the Graduate Council of the
University of North Texas in Partial
Fulfillment of the Requirements

For the Degree of

DOCTOR OF PHILOSOPHY

By

Cynthia Ellen Fincher, B.A., M.S.
Denton, Texas

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This study examined the effect of neurotoxic chemical exposures on brain processes using Single Photon Emission Computed Tomography (SPECT). A control group carefully screened for good health and minimal chemical exposures was compared to two groups of patients diagnosed with health problems following exposure to pesticides or to organic solvents.

A clear decrease was found in the cumulative amount of tracer uptake in the early phase between the control group and the two neurotoxic groups, indicating a decrease in blood flow to the brain. Differences were not detectable between the two neurotoxic groups. In the late phase, which measures metabolic processes or function, a cumulative measure of tracer uptake did not detect differences between the groups. The tracer uptake scores of function for the neurotoxic groups fell outside the range of normal scores in both directions, suggesting that brain function is affected in a complex manner which is undetectable with a single cumulative score. The detected differences in brain

processes occurred at a low-level of chemical exposure in which minimal research has been conducted.

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I would like to acknowledge Mark Fincher, who is my greatest supporter and closest friend, and my father, Forrest G. Riecken (4-12-36 to 11-22-94), whose vision and encouragement inspired me to achieve.

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THE USE OF SINGLE PHOTON EMISSION COMPUTED TOMOGRAPHY TO INDICATE NEUROTOXICITY IN CASES OF PESTICIDE AND SOLVENT EXPOSURES

The use of neurotoxic chemicals in industrial, agricultural, and domestic settings has led to increasing concern about the impact these substances have on neurological functioning (Stone, 1992). A substance is neurotoxic if it is harmful or poisonous to the nervous system (Singer, 1991). Exposure to such a substance can create the condition of neurotoxicity.

Broad classes of chemicals which are recognized to be neurotoxic include pesticides, organic solvents, heavy metals, petroleum products, and formaldehyde (Weiss, 1983; Singer, 1991). The available data on the health impact of these and other widely used chemicals is limited. As recently as 1984, the National Research Council reported that minimal or no information was available on the toxicity of 66% of pesticides and their inert ingredients, 84% of cosmetic ingredients, 64% of prescription drug ingredients, 81% of food additives, and 88-90% or the chemicals in commerce (cited in Ashford & Miller, 1991).

Certain groups of people have been identified as having an increased risk for chronic, low-level toxic chemical

exposure. These groups include industrial workers, occupants of "tight buildings" (including office workers and school children), residents of communities whose air and water is contaminated by chemicals, and individuals who have had personal and unique exposures to various chemicals (in domestic indoor air, pesticides, drugs, and consumer products) (Ashford & Miller, 1991). These groups of people are diverse: including males and females of differing ages and educational levels.

The symptom pattern of classic neurotoxicity includes: fatigue, mental changes (including problems with memory for recent events, concentration difficulties, and mental slowness), headache, numbness in the hands or feet, sleep disturbances, personality changes, and the recognition that there has been a loss of mental function (Singer, 1990, p 3). Lower levels of toxic exposure, however, can have similar effect. Fatigue, apathy, emotional lability, and tremors have been identified in low level, chronic exposures to a variety of toxic compounds. As such, "Under low levels of chronic exposure, the effects are unlikely to be characteristic of a particular compound" (Fein, Schwartz, Jacobson & Jacobson, 1983, p. 1192).

Neurotoxic poisoning may be evidenced initially by psychological symptoms. "Many poisonings, before they bloom into overt clinical signs, may be heralded by vague, subjective, nonspecific psychological complaints." (Weiss,

1983, p. 1174). Thus, psychological measures potentially yield more information than blood tests in detecting neurotoxic damage, as they detect subtle mental alterations earlier than our current technology is able to measure changes in blood chemistry (Weiss, 1983).

In a study of patients with a history of neurotoxic chemical exposure who reported chronic health problems related to the chemical exposures, objective psychological measures were shown to verify the presence of subjectively reported psychological symptoms. A psychological pattern of fatigue, short-term memory loss, and decreased mental functioning was found (Fincher, Harrell, Butler, in press). Following the removal of the implicated neurotoxin, cerebral symptoms have been reported to diminish (Rea, Butler, Laseter, & DeLeon, 1984).

Neurological impairment and response deficits consistently have been found in animals exposed to toxic substances (Hayes, 1982). Subtle symptoms in rats, including an abnormal susceptibility to fear and a violent reaction to stimuli, were found to precede tremors and convulsions in DDT exposures (Domenjoz, 1944, cited in Hayes, 1982). Rats exposed to the pesticide dieldrin and simultaneous inescapable shocks later demonstrated escape deficits relative to controls (Carlson & Rosellini, 1987). Mice exposed to low levels of PCB's prenatally showed longer latencies in response to painful stimulation and

difficulties in tasks requiring perceptual-motor integration even after the PCB's were no longer detectable in their body tissues (Tilson, Davis, McLachlan & Lucier, 1979). Low level perinatal exposures to PCB's in mice have also been shown to result in a sluggish response to stress, an initially depressed response to a novel environment, and a failure to habituate (Storm, Hart, & Smith, 1981).

Pesticides and organic solvents are neurotoxins that are petroleum derivatives composed of simple hydrocarbons or halohydrocarbons (Hayes, 1982, p 118). Workers who are exposed to pesticides comprise one of the largest occupational populations at risk of neurotoxicity in the world (Davies, 1990). Workers exposed to solvents comprise another high risk occupational group. The neurotoxic hazards of solvents has led to the recognition of "solvent syndrome" as an occupational disease in Denmark (Olsen & Seedorff, 1990).

Pesticides can be divided into three broad categories of neurotoxins: the organophosphate pesticides, the chlorinated hydrocarbon insecticides, and the carbamate pesticides. The organophosphate pesticides are the direct descendants of the "nerve gas" compounds used in chemical warfare (Hayes, 1982). The chlorinated hydrocarbons were designed to be longer lasting and less toxic than the organophosphates (Singer, 1991).

Pesticides can be absorbed through the skin, ingested, or inhaled (Hayes, 1982). The World Health Organization has estimated that there are as many as 500,000 acute pesticide poisoning incidents world wide each year (WHO, 1973, as cited in Savage, Keefe, Mounce, Heaton, Lewis, & Burcar, 1988).

Both the organophosphate and the carbamate pesticides act by inhibiting acetylcholinesterase. This enzyme degrades the neurotransmitter acetylcholine. Acetylcholine will initially accumulate and excite the cholinergic receptors, but this initial excitation is followed by a paralysis of the cholinergic nervous system. Acetylcholine is used in the transmission of nerve impulses in the autonomic nervous system (both sympathetic and parasympathetic), the somatic nervous system, and in the central nervous system (Hayes, 1982).

The chlorinated hydrocarbons include DDT, benzene hexachloride, chlordane, lindane, aldrin, and dieldrin. They are toxic to the central and peripheral nervous systems, with effects particularly noted in the cerebellum and the motor cortex (Hayes, 1982, p 191).. DDT has been found in all tissues including the blood, liver, kidney, heart, and central nervous system (Smith and Stohlman, 1944). The highest concentrations are found in the adipose tissue (Ofner & Calvery, 1945).

Subtle neurotoxic effects have been found in cases of prior acute organophosphate poisoning. Neuro-psychological tests were able to detect deficits in intellectual functioning, academic skills, abstraction, flexibility of thinking, and simple motor skills. The Halstead-Reitan Battery revealed that scores in the range of cerebral damage or dysfunction were twice as likely in the organophosphate exposed group as in controls. In addition, the reports of the patients and their relatives revealed ongoing neuropsychological deficits (Savage, Keefe, Mounce, Heaton, Lewis, & Burcar, 1988). Serum and blood analyses and electroencephalogram tests were unable to detect the ongoing impact of the neurotoxins.

The neurotoxic effects of organic solvents has been labeled the "solvent syndrome" (Olsen & Seedorff, 1990). Symptoms resulting from solvent exposure can include dizziness, nausea, and weakness (Gyntelberg, Vesterhauge, Fog Isager, & Zillstorff, 1986), fatigue, problems with arm strength, and feeling "high" (Fidler, Baker, & Letz, 1987), intoxication, incoordination, exhilaration, sleepiness, stupor, and early anesthesia (Dick, 1988), visual disorders (Takeuchi, 1988), sleep apnea and insomnia (Monstad, Nissen, Sulg, & Mellgren, 1987; Lindelof, Almkvist, & Gothe, 1992), alterations in cognitive functioning, and personality changes (Morrow, Ryan, Hodgson & Robin, 1990). Cognitive deficits are found in measures of memory and learning,

visuospatial ability, attention and mental flexibility, and psychomotor speed (Morrow et al., 1990).

Neuropsychological testing of workers exposed to organic solvents indicated a significantly poorer performance on the forward digit span test, copying of a complex figure, and on semantic memory tests which also measure the ability to integrate linguistic information into cohesive units (Milanovic, Spilich, Vucinic, Knezevic, Ribaric, & Mubrin, 1990). Other researchers found that performance on tests of digit symbol and digit span corresponded with the level of exposure to organic solvents in construction painters (Fidler, et al., 1987). The MMPI profile for organic solvent exposure shows significant levels of depression, anxiety, somatic concerns, and disturbances in thinking (Morrow et al., 1990).

The symptom pattern resulting from organic solvent exposure has been consistent across cultures. A study of Chinese printing and paint workers reported that the workers experienced symptoms of fatigue, irritability, depression, poor memory, sleep disturbances, and symptoms suggestive of autonomic dysfunction. The performance of the exposed workers as compared with appropriate controls on neurobehavioral tests was significantly poorer on digit symbol and choice reaction test (which measure psychomotor function) and on digit span and associate learning (which measure auditory memory) (Ng, Ong, Lam, & Jones, 1990).

Some of the effects of organic solvents on workers are reversible, if the individual is removed from the exposure (Dick, 1988). Most cognitive functions improve with cessation of exposure, with the notable exception of memory (Hanninen, 1988). Recovery is most likely in cases where workers report symptoms, but demonstrate no impairment on neuropsychological tests. In cases of toxic encephalopathy, where symptoms were reported and there was impairment in test performance, ongoing central nervous system effects were present five years later (Edling et al., 1990).

Several techniques have attempted to objectively detect the presence of neurotoxins. One study of neurological alterations caused by organic solvents utilized a neurological examination, neuropsychological testing, electroencephalography (EEG), electromyography (EMG), and cerebral computerized tomography (CT). The neuropsychological testing demonstrated marked reductions in functioning, particularly in short-term memory. The neurological testing, the EEG, and the CT revealed only minor abnormalities (Berstad, Flekkoy, & Pedersen, 1989).

A study utilizing auditory, visual, and somatosensory evoked potential EEG testing found that this technique was only able to detect neurotoxicity to a slight degree on the somatosensory evoked potentials. The peripheral conduction velocities showed a slight decrease and the central conduction times showed an increase in conduction (Massioui,

Lille, Lesevre, Hazemann, Garnier, & Dally, 1990). In peripheral nerve conduction velocity (NCV) testing, the integrity of the peripheral nerve is determined by measuring the latency and the amplitude of the nerve response (Singer, 1990). This technique, however, is not able to measure central nervous system deficits.

Neurotoxic chemicals affect both the brain and the peripheral nervous system (Singer, 1990). In order to detect the presence of neurotoxins, a technique is needed to assess brain functioning. Currently, performance measures on neuropsychological tests appear to be the most accurate technique to measure the effects of neurotoxicity. The lack of a respected medical technique that can objectively measure neurotoxicity is a significant problem in the field of chemical injuries.

One of the rapidly growing techniques in brain research is Single Photon Emission Computed Tomography (SPECT) (Stephenson, 1990). SPECT imaging measures regional cerebral blood flow (rCBF) by measuring the uptake of a radiopharmaceutical (like Technetium-99m hexamethylpropyleneamine oxime) in the blood and in the brain tissues. In this manner the SPECT scan measures both blood <u>flow</u> through the arteries and veins (able to detect ischemias) and <u>function</u> (ie metabolism into the tissues) of the blood products. The flow is measured in an early image state and the function is measured in the late image set by

trapping the tracer in the neurons through a glutathione mediated process that changes the initially lipophilic tracer into a hydrophilic molecule.

SPECT is likely to be more useful than a computed tomography (CT) image in detecting neurotoxicity because it is able to measure dynamic brain functioning, while the CT measures static anatomical structures. A SPECT image has similarities to a PET, but SPECT is a more suitable technique because it is less costly and a less elaborate procedure to perform (Gemmell et al., 1990). Traditionally, PET has been thought to have a superior resolution to SPECT (Kolb & Whishaw, 1990). The quality of the resolution is dependent on the tracer and the imaging strategy. Recent advances in technology have resulted in comparable resolution in practice.

SPECT has been used in studies of patients with epilepsy (Ryding, Rosen, Elmquist & Ingvar, 1988; and Shen, et al. 1990), head injuries (Abdel-Dayem et al., 1987), cerebral palsy (Denays, 1990), dementias (Costa, Ell, Burns, Philpot, & Levy, 1988), drug use (Holman, 1991; Tumeh, Nagel, English, Moore, & Holman, 1990), depression (Mathew, Meyer, Francis, Semchuk, Mortel, & Claghorn, 1980), and schizophrenia (Berman, Weinberger, Shelton, & Zec, 1987). It has even been used in patients diagnosed with obsessive-compulsive disorders and eating disorders (Stephenson, 1990). In a comparison study of SPECT and CT scans on

patients with acute head injuries, the Tc-99m HMPaO SPECT was found to be more sensitive than the CT in demonstrating lesions at an earlier stage and in separating lesions which had a favorable prognosis from those with an unfavorable prognosis (Abdel-Dayem et al., 1987). In another study, the Tc-99m HMPaO SPECT scan was used to differentiate between dementia of the Alzheimer type (DAT) and multiinfarct dementia (MID) (Gemmell et al., 1987). SPECT has been found to be useful in early diagnosis of HIV encephalopathy in cases where CT and magnetic resonance (MRI) were unrevealing (Masdeu et al., 1991).

Because this technique is able to detect whether brain regions are abnormal prior to overt structural damage, it has the potential to uncover subtle neurological changes. It could detect the abnormalities in brain functioning which are demonstrated in neuropsychological testing. This technique could allow accurate, early diagnosis of neurotoxicity by an objective physiological measure.

Based upon clinical observations and pilot studies using this technique, the following hypotheses were made: 1) Flow was predicted to be decreased in people exposed to neurotoxins. 2) Function (as defined by measuring the late image set) scores were predicted to fall outside the normal range. 3) The relationship between flow and function in an individual was predicted to be mismatched, so that a decrease in one measure would result in an increase in the

other measure. Therefore, the ratio between the numerical values assigned to flow and to function in neurotoxic exposures was predicted to be different from the ratio in controls. The current study sought to verify or disconfirm these hypotheses.

METHOD

Subjects

The subjects were selected from the patient population at Advanced Metabolic Imaging Center in Dallas. A total of 25 controls and 40 patients were selected based upon their history of exposure.

The control group was composed of 25 healthy volunteers who met the health qualifications of a stringent questionnaire (Appendix A). The volunteers came from the Dallas community and were recruited primarily from the student population at the University of North Texas and from local churches. The questionnaire screened for medical history, drug usage, medication usage, chemical exposure, family history, and symptoms that could indicate neurologic injury. The age range of the control subjects was 25 to 45 years of age. There were 15 female and 10 male subjects evenly distributed across four-year age ranges, with three women and two men in each age grouping (25-28, 29-32, 33-36, 37-40, and 41-45). A more extensive description of this control group is given in Fincher, Simon, Kettelhut, Hickey, and Harrell (In preparation).

The patients with neurotoxic exposure were referred for a SPECT study by doctors at the Environmental Health Center of Dallas. The medical history, laboratory results, and diagnoses of the patients were made available for the purpose of classifying them by type of exposure. The criterion for selection into the study was based upon a case history in which an adult in the appropriate age range experienced good health prior to a specific instance of toxic exposure. Patients with complex pre-existing medical conditions were not selected. An exposure history in which multiple toxins from various classifications of chemicals was unacceptable. The acceptable age range of patients was between 20 and 50, in order to be comparable with the control group.

Of the approximately 450 cases reviewed, 15 were qualified to represent pesticide exposures. A case history of a specific exposure to pesticides was required. Table 1 contains an abbreviated history of each of the patients selected. There were 10 females and 5 males selected ranging in age from 24-46, with an average age of 37.6. Although a blood analysis was available on some of the patients, this was not judged to be a reliable measure of pesticide exposure due to the known rapid metabolism of organophosphate pesticides (Hayes, 1982). The length of

Table 1

Exposure Histories of Pesticide Subjects and Time Period to Initial Symptoms or Hospitalization**

Dursban Exposed Patients

1) Exposure over 2 day period to home professionally treated with Dursban resulted in emergency hospitalization
2) Exposed when home treated with Dursban. Symptoms began following the fourth treatment over a four year period
3)* Exposed 1 day when professional application of Dursban was injected into ground around home and into water supply. Drank contaminated water
4)* Exposed 1 day when professional application of Dursban was injected into ground around home and into water supply. Drank contaminated water
5)* Exposed 1 day to misapplied Dursban by professional exterminator. Left house after first night, but wiped up puddles of pesticide with rags over later days. Spouse was dead within 2 weeks of incident

Chlordane Exposed Patients

6) Exposed over 3 month period when moved into a house previously treated with chlordane
7) Exposed over 7 year period by living in a home treated with chlordane
8) Exposed a total of 3 years from living in a residence treated with chlordane. Symptoms experienced after 6 months
9) Exposed to a chlordane treated house over a several year period. Symptoms abated when relocated, but became severe when carpeting at new residence was treated with pesticides
10)* Professional misapplication of pesticides in which high levels of heptachlor were detected in house following "clean-up effort". Both chlordane and Dursban used

Other Pesticides

11) Exposed over one day to pesticide bomb in home
12) Exposed 1 day when pesticide used on house to treat fleas
13) Exposed when treated own home with pesticides

(Table Continues)

14) Exposed over 3 days doing farm work applying 150 lbs of malathion over 3 day period
15) Exposed over a ten year period while working with animals and applying pesticides to their cages

*This represents an inappropriate application and unusually high level of exposure.
**In cases where the patient's home was contaminated, there may have been additional, ongoing exposure following the initial attack if they did not move from their place of residence.

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time from the development of symptoms to the SPECT ranged from two months to twelve years, with an average time of four years and five months.

The selection criterion for the solvent group included both a history of good health prior to a defined organic solvent exposure and a detectable level of solvents measured in a blood analysis performed by Accu-Chem laboratories. Accu-Chem panels 4A and 6, which detect solvents, are shown in Appendix B. In cases in which multiple blood levels were drawn, the blood test which best corresponded to the date of the SPECT scan was recorded. Table 2 contains a brief history of each of the patients selected for the solvent exposure group. Twenty-five people were selected: 13 males and 12 females, aged 23 to 49 with an average age of 39.4. The length of time for the development of symptoms to the SPECT scan ranged from one month to eight years, with an average time span of two years and six months.

Table 2

Exposure Histories of Solvent Subjects and Time Period to Initial Symptoms or Hospitalization

---

Occupational Exposures With Solvents in Daily Use

1) Exposed over 2-3 year period to chemicals used in developing film. Symptoms began approximately 1 year into exposure
2) Exposed over 1-2 year period while working for a chemical company mixing chemicals together in 1,500 gallon vats. Symptoms began approximately 1 year into exposure
3) Exposed over 4 months when moved to a position which required cleaning airplane parts with solvents, following seven years of employment with company. Chemicals involved were N-butylacetate, Propylene Glycol Methyletheracetate, and Isoparaffinic Compound
4) Exposed over a 6-7 year period working as a nurse in a dialysis unit during an eight year career.
5) Exposed over a 9 year period as a printer. Symptoms began during the fourth year
6) Exposed over a 4 year period to a phenol based disinfectant used in a hospital. Emergency room visits began after 2 years
7) Exposed for at least 1 year while working in a machine shop which used solvents to clean parts
8) Exposed for years in work as a mechanic utilizing solvents to clean parts
9) Exposed for 2-3 years working with solvents, including hydrozene, and alcohol.

Unusual Occupational Exposures

10) Exposed over 1 hour when performing emergency medical services on a man who had been heavily exposed to ethylene dichloride
11) Exposed 1 hour to solvents on rags used to degrease airplane parts at job as a dry cleaner. Chemicals identified included toluene, ethylbenzene, and methylethyl ketone
12) Exposed 2 days to a chemical spray while repairing pipes at a construction site. Chemicals identified included: isocyanide, ammonia, MHBA, hydrolyzate and solvent, methyl isobutyl detone, hydrotencyanide, and organic sulfides

(Table continues)

13) Exposed 2 days to a chemical spray while repairing pipes at a construction site (see chemicals listed for
14) Exposed 2 days to a chemical spray while repairing pipes at a construction site (see chemicals listed for 12)
15) Exposed 1 day to a chemical spray while repairing pipes at a construction site (see chemicals listed for 12)

Tight Building Syndrome

16) Exposed 1 month during a renovation in an office to carpet glue, carpeting, solvents and paints
17) Exposed 1.5 years working in a "tight" or toxic building.
18) Exposed for 6 weeks while working in an office in which trimethylbenzene and other solvents were used to remove floor tiling
19) Exposed for 3 years to a newly constructed "tight building"

Contaminated Ventilation Systems

20) Exposed 1 year working in a tight building in which the ventilation system was pulling in contaminated air and which was undergoing reconstruction
21) Exposed for 2.5 years to a gas leak in home (note: job required frequent travel from home)
22) Exposed for 6 months to methylmethacrylate and xylene leaking into vent system while working in a hospital
23) Exposed for 4 months in home during remodeling and leakage of sewer gases into home. Symptoms began after 1 month

Environmental Disasters

24) Exposed for 6 hours prior to evacuation from a chemical spill officially reported as containing 60,000 tons of chlorine
25) Exposed during summer months while working in an environmental clean-up effort of an Alaskan tanker spill. Exposed to Inapool (solvent) and petroleum

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Procedure

After signing informed consent forms, the patients were given a Mini-Mental Status Exam (see Appendix C). This abbreviated psychiatric test is able to detect gross

neurological deficits (Folstein, Folstein, & McHugh, 1975). The subjects were then tested using Tc-99m HMPaO SPECT with a triple-headed gamma camera.

Each patient was injected with approximately 25 millicures of technetium-99m HMPaO using a Harvard pump for tracer delivery. A triad [Trionix] triple headed gamma camera was used for data collection. The images were acquired into a 128 x 128 pixel matrix for 28 minutes. An initial series of images was obtained during the injection as a measure of cerebral blood flow. After approximately fifteen minutes, a second series of SPECT images was obtained. This second, late image set illustrates the trapping of the tracer in the neurons through a glutathione mediated process that changes the initially lipophilic tracer into a hydrophilic molecule. It is a measure of function.

The images were computer processed, filtered and back-projected onto three planes orthogonal to the canthomeatal plane. The resulting computer file contains a complete three dimensional representation of the brain functioning. Slices can be taken from any angle and interpreted for their activity. The level of metabolism is represented by the pixel density, or the brightness of the light readings.

These images were interpreted quantitatively by reducing the mathematical matrices that represented the local tracer distribution. This analysis was conducted

radially from the transverse projection. The initial information was taken in two degree increments. The increments were summed into 360 degree intervals for the a priori analysis and into 60 degree intervals for more detailed later comparisons.

Three slices of interest were selected to compare brain activity in the frontal lobe, the limbic system, and the temporal lobe. The most superior transverse slice in which the thalamus became visible was selected to represent limbic lobe activity. The slice immediately superior to this slice was selected to represent frontal lobe activity. Temporal lobe activity was represented by the fourth coronal slice in which the temporal structures were visible. This slice was labeled coronal.

RESULTS

For each subject, measurements were taken from three slices labeled "coronal", "frontal" and "thalamic", as described above. The means, standard deviations, and the range of flow are shown for each group in Table 3, and Table 4 contains these values for function. The means of the groups are displayed in graphic form in Appendix D. As can be seen in Table 4, the pesticide exposure group contained function scores which were more extreme than the control group in both directions. The solvent group had more extreme minimum and maximum values in the coronal and

Table 3

Frequencies and Means of Flow Tracer Uptake For Each Slice

LEVEL	GROUP	Min Value	Max Value	Stan Dev	Mean
Coronal	Controls	351959.0	933327.0	159883.3	595460.7
	Pesticide	279998.0	839805.0	148945.7	485186.7
	Solvents	264945.0	773022.0	148042.1	466523.4
Frontal	Controls	450686.0	1224653.0	198750.1	810389.3
	Pesticide	388589.0	1142266.0	200872.8	675505.8
	Solvents	362445.0	1066601.0	194957.3	650678.6
Thalamic	Controls	507919.0	1269024.0	202352.5	849625.4
	Pesticide	413450.0	1195295.0	206505.7	709776.7
	Solvents	387667.0	1106120.0	202152.7	683304.5

frontal slice. The standard deviation was greater in the neurotoxic groups than in the control group.

Differences among the three groups in the total counts of tracer activity for each slice were analyzed with one-ways ANOVA's. Six one-way ANOVA's were performed on the entire 360 degree slices, three for flow and three for function. The results are show in Table 5.

Differences in tracer uptake in counts for flow were found to be significant for all three slices. Function, however, was not significant in any case. In post hoc analyses using the

Table 4

Frequencies and Means of Function Tracer Uptake For Each Slice

LEVEL	GROUP	Min Value	Max Value	Stan Dev	Mean
Coronal	Controls	1789476.0	3708798.0	534404.6	2580611.4
	Pesticide	1429075.0	4228928.0	792151.1	2373469.9
	Solvents	1283676.0	3769599.0	747145.6	2142248.3
Frontal	Controls	2606279.0	5158952.0	703600.2	3639766.4
	Pesticide	2097819.0	5990405.0	1067387.2	3448645.7
	Solvents	1988961.0	5340568.0	1065353.5	3144305.7
Thalamic	Controls	1607362.0	5383333.0	835620.5	3730573.0
	Pesticide	1389520.0	6077208.0	1157244.7	3531892.1
	Solvents	2102793.0	5606672.0	1102068.3	3284615.8

Newman-Keuls Test, flow was found to significantly differentiate the control group from both of the neurotoxic exposure groups. Flow between the neurotoxic groups was not significantly different.

Discriminant Function Analysis was utilized to determine whether the three groups could be correctly classified based upon the tracer activity values of flow and function. The analysis classified the subjects into the groups at each of the three slices for flow and for function. Table 6 shows the percentage of each of the three groups which were correctly classified

Table 5

Analysis of Variance For Each Slice

Measure	Slice	F-Value	Pr > F
Flow	Coronal	4.96	0.0100*
	Frontal	4.52	0.0147*
	Thalamus	4.64	0.0133*
Function	Coronal	2.57	0.0850
	Frontal	1.75	0.1826
	Thalamus	1.20	0.3095

* indicates significance

Table 6

Discriminant Function Analysis Percentage of Correctly Classified Cases For the Three Groupings

Measure	Slice	Control	Pesticide	Solvent	Pr > F
Flow	Coronal	72%	53.3%	52%	.0100*
	Frontal	72%	53.3%	60%	.0147*
	Thalamic	68%	66.7%	68%	.0133*
Function	Coronal	68%	66.7%	64%	.0850
	Frontal	72%	73.3%	76%	.1826
	Thalamic	60%	60%	64%	.3095

in the Discriminant Function Analysis. All of the slices were found to be classified with significant accuracy for the Flow measure. The Function measure was not found to be able to differentiate the groups with statistically significant accuracy, although the majority of cases were correctly classified.

In another Discriminant Function Analysis in which the pesticide and solvent groups were combined into a single group labeled neurotoxic, all three levels of flow and the coronal measure of function were found to significantly differentiate the control group from the neurotoxic exposure

Table 7

Discriminant Function Analysis Percentage of Correctly Classified Cases

Measure	Slice	Controls	Neurotoxic	F-Value	Pr > F
Flow	Coronal	60%	70%	9.9160	.0025*
	Frontal	64%	70%	9.0190	.0038*
	Thalamic	60%	72.5%	9.2348	.0035*
Function	Coronal	60%	70%	4.0577	.0482*
	Frontal	68%	62.5%	2.5195	.1175
	Thalamic	60%	57.5%	1.8539	.1782

*indicates significance

group. The frontal and thalamic measures of function were not found to be statistically significant. Table 7 shows the percentage of each group which was correctly categorized and the significance level of the measure.

An Analysis of Variance procedure was performed on the scores of the Mini-Mental Exam. A perfect score on this exam is 30. The mean of the control group was 29.6. The mean of the pesticide group was 28.4, and the mean of the solvent group was 28.6. The results are shown in Table 8. A significant difference was shown (F = 7.26. Pr > F 0.0018). The Newman-Keuls analysis revealed that both of the neurotoxic exposure groups were significantly different from the control group, but were indistinguishable from one another. None of the scores obtained by the three groups, however, would be considered pathological. In a study introducing the Mini-Mental Exam, a mean score of 27.6 was found for the normal subjects. Pathological mean scores of

Table 8

Analysis of Variance For Mini Mental Exam Scores

Group	n	Mean
Control Group	21	29.6190
Pesticide Exposure	13	28.3846
Solvent Exposure	17	28.5882

25.1 were found for depression, 19.0 for depression with cognitive impairment, and 9.7 for patients with dementia (Folstein, Folstein, & McHugh, 1975).

Following the main analyses of the data, further explorative examinations were performed. Tables 9 and 10 present the means of each of the sixty degree sectors within the three slices for flow and for function.

ANOVA comparisons of the individual sectors and the significance levels are shown in Tables 11 and 12. As can be seen Table 11, when compared by sector, significant differences in flow were found in almost every sector. In contrast, when comparing sectors for function, no significant differences were found in any of the six sectors in the frontal or the thalamic slice. In the coronal slice, the left lateral sector (L 2) and the left inferior sector (L 3) showed significant differences. Function in the left inferior coronal sector (L 3) of the solvent patient group was significantly less than that of the control group. In the pesticide group, the left interior coronal sector (L 3) function was less than the control group, but was not significantly different from either the control group or the solvent group.

A comparison of the ratio between flow and function did not reveal differences between the groups. Table 13 shows the mean of the ratios for each group for each slice. None of the ANOVA's performed were significant.

Table 9

The Mean Count of Tracer Activity For Flow For Each of the Sectors

	* L 1	L 2	L 3	R 1	R 2	R 3
Coronal						
Control	102632	111193	87912	101459	105689	86573
Pesticide	88805	87847	69264	85064	85977	68226
Solvent	84550	84951	68045	79257	81405	68313
Frontal						
Control	131510	128575	148907	135526	123262	142606
Pesticide	113452	106838	123304	112025	102605	117279
Solvent	109725	103172	118097	106033	98298	115352
Thalamic						
Control	136474	136514	153897	141570	131884	149285
Pesticide	118110	114921	126576	117686	110653	121828
Solvent	114850	111821	122205	111148	104802	118476

*L=Left

R=Right

1=anterior section superior for coronal

2=lateral section

3=posterior section inferior for coronal

Table 10

The Mean Count of Tracer Activity For Function For Each of the Sectors

*	L 1	L 2	L 3	R 1	R 2	R 3
Coronal						
Control	445540	492383	354088	454888	478387	355323
Pesticide	434308	449137	312773	422298	437654	317297
Solvent	399171	401245	272426	393249	393420	282734
Frontal						
Control	587311	581474	646130	624456	569714	630680
Pesticide	581399	537139	604342	590441	543832	591490
Solvent	531831	502105	552543	528216	486351	543257
Thalamic						
Control	618041	615587	641503	636993	590317	628128
Pesticide	596930	572480	607236	604397	562242	588607
Solvent	556131	537253	564366	552051	519832	554983

*L=Left

R=Right

1=anterior section superior for coronal

2=lateral section

3=posterior section inferior for coronal

Table 11

Analysis of Variance of Flow Tracer Activity For Each Slice

Slice	Section	F-Value	Pr > F
Coronal	*L 1	3.32	.0426
	L 2	6.71	.0023
	L 3	4.26	.0185
	R 1	4.95	.0101
	R 2	5.70	.0053
	R 3	3.70	.0302
Frontal	L 1	2.98	.0580
	L 2	4.51	.0149
	L 3	4.86	.0110
	R 1	5.61	.0057
	R 2	4.70	.0125
	R 3	4.18	.0198
Thalamic	L 1	2.78	.0697
	L 2	3.91	.0251
	L 3	5.51	.0086
	R 1	5.54	.0061
	R 2	4.97	.0100
	R 3	5.15	.0086

*L=Left
R=Right
1=anterior section superior for coronal
2=lateral section
3=posterior section inferior for coronal

Table 12

Analysis of Variance of Function Tracer Activity For Each Slice

Slice	Section	F-Value	Pr > F
Coronal	*L 1	0.96	.3877
	L 2	3.21	.0471
	L 3	3.83	.0270
	R 1	1.65	.1996
	R 2	3.06	.0539
	R 3	2.75	.0718
Frontal	L 1	0.91	.4081
	L 2	1.81	.1728
	L 3	1.18	.1721
	R 1	2.45	.0950
	R 2	2.07	.1354
	R 3	1.64	.2020
Thalamic	L 1	0.93	.4016
	L 2	1.40	.2533
	L 3	1.06	.3540
	R 1	1.55	.2196
	R 2	1.14	.3261
	R 3	1.00	.3741

*L=Left
R=Right
1=anterior section (superior for coronal)
2=lateral section
3=posterior section (inferior for coronal)

Table 13

The Means of the Ratio of Tracer Activity For Flow to Function

Slice	Group	Mean
Coronal	Controls	0.2287848
	Pesticides	0.2040140
	Solvents	0.2223229
Frontal	Controls	0.2229828
	Pesticides	0.2083025
	Solvents	0.2208165
Thalamic	Controls	0.2420952
	Pesticides	0.2153387
	Solvents	0.2168304

A high correlation was found between the three measures of flow, indicating that a measure of flow taken from one of the slices is highly representative of flow in the other slices. These three correlations were all significant at the .0001 level. Correlations between the function measures produced the same results (see Table 14).

Table 14

Pearson Correlation Coefficients Between Measures of Flow and Measures of Function

Comparison	Correlation	Sig Level
Coronal to Frontal Flow	.95279	.0001
Frontal to Thalamic Flow	.99501	.0001
Thalamic to Coronal Flow	.95900	.0001
Coronal to Frontal Function	.94583	.0001
Frontal to Thalamic Function	.95607	.0001
Thalamic to Coronal Function	.90414	.0001

DISCUSSION

The results of this study show decreased brain blood flow in patients seeking medical care following an exposure to pesticides or organic solvents. The pattern of decreased flow was highly significant in all of the slices which were analyzed, and it was present in almost every sector of each slice.

The differences in flow between the control group and the groups with known neurotoxic exposures were of sufficient magnitude for the exposure group to be correctly classified about 70% of the time based solely on the SPECT measure of flow. The known neurotoxicity of these

substances is highly implicated in the altered level of brain blood flow.

The data in the present study suggests that the tracer uptake for flow and for function do remain proportionally related to one another. A mismatch between the two processes in which decreased flow corresponded with increased functioning or increased flow corresponded with decreased functioning was not detected.

The relationship between neurotoxic exposure and brain function is more complex. The measure of brain function illustrates the trapping of the tracer in the neurons over time. It is a glutathione mediated process in which the initially lipophilic tracer changes into a hydrophilic molecule. The visual images which were used to select the slices for numerical analysis showed marked dissimilarities between the groups. In the statistical analysis, however, no significant relationship was found in the comparison of the total scores for each slice. When utilizing the function score alone to determine group membership, only the coronal slice was able to classify subjects accurately to a statistically significant degree.

A more sophisticated method of data summary will be required to determine which of several hypotheses regarding the function measure is accurate. It is possible that no relationship exists between neurotoxic exposures and brain functioning. This hypothesis does not explain the evident

visual differences in the images which are generated for clinical diagnosis, nor does it account for the ability of discriminant analysis to correctly place the majority of subjects. Another hypothesis is that abnormal function measures at both the high and low extremes of the distribution are canceling out differences in the function measure. As can be seen in Table 4, the minimum and maximum values of tracer uptake for function for the pesticide exposure group and the solvent exposure group are consistently more extreme than the range of values of the control group. The standard deviations of both neurotoxic groups are greater than the control group. The bidirectional departure from the normal range of scores is not reflected in the group means.

An additional complication in accurately assessing the data on function is that abnormal levels of activity--both high and low extremes--within the same person cannot be detected by the present method of data collection. An examination of the visual images reveals that many of the images for the patient groups were abnormally bright at the center of the image and darker at the outer part of the sphere. The wedge-shaped units of measure make detection of interior versus exterior differences in tracer uptake impossible. Alternate methods of finer data summary will be necessary to more accurately examine the impact which neurotoxic exposure exerts on brain function.

Further studies will need to consider another hypothesis, which is that neurotoxic exposures may result in bidirection abnormalities in brain function. The chemical composition of the exposure substance may determine whether function is increased, decreased, or within normal limits. Time parameters such as length of exposure and length of delay from exposure to SPECT imaging also may be important in such an investigation. The known action of cholinesterase inhibitors, for example, is an initial increase in acetylcholine followed by exhaustion of the system and a lowered response. A pattern of initial activation and an ensuing reduction in functioning is a possibility for a single substance. The complexity of this field of study requires direct measures of neurological alterations, such as SPECT imaging.

Although the utility of highly sophisticated neuropsychological testing in detecting behavior and performance deficits in cases of neurotoxicity has been recognized (Weiss, 1983), the data in the current study suggests that even a crude measure like the Mini-Mental Exam may detect slight differences. This abbreviated exam does not approach the complexity and ability to detect subtle defects of a full neuropsychological battery, and yet it was able to differentiate a statistically significant difference between the control group and the neurotoxic exposure groups. This finding corresponds to previous research

findings of the usefulness of psychological batteries in detecting neurotoxicity. Whether decreased blood flow to the brain causes decreased mental functioning, or whether both are the consequence of a physiological process set in motion by the presence of the neurotoxin is unclear at this time.

It is of particular importance to note that the exposures experienced by the patients in this study generally are not regarded as representing a health hazard. The clear decrease in brain blood flow which was detected occurred at a level of exposure which has received minimal study. The fact that alterations in brain processes are detectable in cases of low-level exposures indicates the need for more thorough investigations of the impact which xenobiotics have on human nervous system functioning.

The interaction between the actual chemical exposure and the unique characteristics of the individual exposed is maximized at lower levels of neurotoxic exposure. It is likely that individual differences in genetics, metabolic processes, general health, age, and gender all influence the susceptibility of any given person.

The careful screening of both the patient groups and the control group to eliminate as many extraneous factors as possible allowed for the best chance of detecting changes solely as a result of neurotoxic exposures. The control group was selected based on being healthy and free of excess

chemical exposures. They were selected to provide a range of tracer uptake counts for people who are symptom-free, rather than representing a random sampling of the population. The patient groups were selected to be free of prior poor health or chronic pain conditions and current additional diagnoses which have the possibility of affecting the brain. The selection process is likely to have increased the difference between the control group and the chemically exposed group, as the control group represents people who are healthier than a random sampling of the population.

In conclusion, this study has begun the process of researching the effects of low-level exposure to neurotoxins on the brain using SPECT data. The fact that a significant difference was found in the level of blood flow in this initial study is clear evidence that SPECT holds potential to further our understanding of the brain and of the impact of foreign chemicals on brain processes. This study is able to suggest abnormalities in function tracer uptake, with both increased and decreased tracer uptake being present. The fact that a detectable difference in brain blood flow has been demonstrated in cases of low-level neurotoxic exposures which are generally regarded as safe is a significant finding which necessitates further investigation.

APPENDIX A

QUESTIONNAIRE USED TO SELECT CONTROL SUBJECTS

NAME_____ AGE_____yrs.
(last) (first) (MI)

ADDRESS_____ PHONE_____

HEIGHT_____inches WEIGHT_____lbs. SEX: male female

EDUCATION: elemetary high school college graduate degree

MEDICAL DIAGNOSIS_____

How many days a year do you miss work due to illness?_____

What medications do you take?_____

What medications have you taken in the past?_____

What kinds of over-the-counter medications and pain killers do you take?

_____

How often do you take over-the-counter medications and pain killers?

_____

How many cups of coffee and/or soft drinks with caffeine do you drink each day? _____

please list them:_____

How many drinks and/or food products which contain Nutra-Sweet do you consume each day? _____

please list them:_____

Do you drink alcohol? Yes No Did you in the past? Yes No

If yes, list what kind, how much per week, and how often (or how long ago).

_____

Do you smoke? Yes No Did you in the past? Yes No

If yes, list what kind, how much per week, and how recently (or how long ago).

_____

Do you use illicit drugs? Yes No Did you in the past? Yes No

If yes, list what kind, how much per week, and how recently (or how long ago).

_____

Are you sensitive to chemicals? Yes No _____
(list which ones)

What chemicals are used at your job?_____

What chemicals are used in your home?_____

Do you notice that when you inhale certain chemicals you experience headaches, nausea, etc.? Yes No

If yes, which ones?_____

Do you wear glasses or contacts? Yes No

If yes: far-sighted near-sighted stigmatism other

If yes, please explain your vision problems_____

Are you: left-handed right-handed both

Are you currently pregnant? Yes No Unsure

Have you ever been pregnant? Yes No How many times?_____

Are you currently breast feeding? Yes No

Are you taking birth control pills? Yes No _____ (list type)

Have you ever had breast implants? Yes No _____ (list type)

Check if you have ever had any of the following:

____seizure
____head injury
____Parkinsons's
____other neurological problems
____tumor
____multiple sclerosis
____schizophrenia
____stroke
____major depression
____learning disability (dyslexia)

Check if you suffer from any of the following:

____severe or recurrent headaches
____vascular problems
____tingling
____joint pain
____chronic high fever
____loss of memory
____depression
____heart condition
____fatigue
____digestive problems
____chronic sore throat
____chemical sensitivities
____chronic yeast infections
____other
____weakness
____respiratory problems
____numbness
____allergies
____chronic viral infections
____memory dysfunction

Check if you have ever been diagnosed with any of the following:

____epilepsy
____hypoglycemia
____lupus (or other collegen disease)
____diabetes
____environmental illness
____Epstein-Barr
____chronic fatigue syndrome
____HIV/AIDS

Have you ever been hospitalized for any reason? Explain_____

_____

Have you ever been unconscious? Explain_____

_____

How long has it been since you have had an x-ray for any reason (including dental)?_____

Check if anyone in your family has:

____seizures
____schizophrenia
____other neurological problems
____Parkinson's
____multiple sclerosis
____other psychiatric problems
____alzheimers
____major depression

Check if you have ever taken:

____diuretics (water retention pills)
____anti-coagulation medications (to prevent blood clotting)
____anti-hypertensives (blood pressure medication)
____steroids
____tranquilizers
____anti-depressants
____psychiatric medications
____other

APPENDIX B

ACCU-CHEM LAB PANELS FOR DETECTING SOLVENTS

ACCU-CHEM LABORATORIES.

The Gold Standard of Testing

LABORATORY REPORT

A Division of
E.H.S Inc.
9901 Bowser
Suite 800
Richardson, TX 75081
(214) 234-5412
1-800-451-0116

PATIENT NAME _____ REFERRING PHYSICIAN/OFFICER _____

SAMPLE IDENTIFICATION _____ HOSPITAL/LAB _____

ANALYZED BY _____ REVIEWED BY _____ STREET ADDRESS _____

DATE COLLECTED _____ DATE RECEIVED _____ CITY/STATE/ZIP _____

DATE ANALYZED _____ PHONE NUMBER _____

P A N E L 6
VOLATILE ALIPHATIC PANEL

Type of Specimen
Blood

Compound	Results ng/ml (ppb)	Accu-Chem Population Average	Detection Limit ng/ml (ppb)
n-Pentane	<1.0	<1.0	1.0
2,2-Dimethylbutane	<1.0	<1.0	1.0
Cyclopentane	<1.0	<1.0	1.0
2-Methylpentane	<1.0	16.3	1.0
3-Methylpentane	<1.0	37.7	1.0
n-Hexane	<1.0	11.7	1.0
n-Heptane	<2.0	<2.0	2.0

Results - parts per billion of the analyzed compound
Population Average - The arithmetic mean derived exclusively from the U.S. population segment tested by Accu-Chem Laboratories.

(Statistical Update 5/24/91)
Average variability factor calculated from 4 ppb level of the above compounds: +/- 26.5%
The average variability factor will increase above 26.5% as results approach the detection limit.

John L. Laseter, Ph.D.
Director of Laboratory

CLIENT COPY

ACCU-CHEM LABORATORIES.

The Gold Standard of Testing

LABORATORY REPORT

A Division of
E.H.S Inc.
990 Bowser
Suite 800
Richardson, TX 75081
(214) 234-5412
1-800-451-0116

PATIENT NAME

REFERRING PHYSICIAN/OFFICER

SAMPLE IDENTIFICATION

HOSPITAL/LAB

ANALYZED BY REVIEWED BY

STREET ADDRESS

DATE COLLECTED DATE RECEIVED

CITY/STATE/ZIP

DATE ANALYZED

PHONE NUMBER

PANEL 4A
VOLATILE AROMATIC & CHLORINATED HYDROCARBONS

Type of Specimen: Blood

Compound	Results ng/ml (ppb)	Accu-Chem Population Average	Detection Limit ng/ml (ppb)
Benzene	<1.0	<1.0	1.0
Toluene	<0.5	2.1	0.5
Ethylbenzene	<0.5	<0.5	0.5
Xylenes	<1.0	<1.0	1.0
Styrene	<1.0	1.0	1.0
Trimethylbenzenes	<1.0	<1.0	1.0
Dichloromethane	<1.0	<1.0	1.0
Chloroform	<1.0	1.0	1.0
1,1,1-Trichloroethane	<0.5	1.0	0.5
Trichloroethylene	<0.5	<0.5	0.5
Tetrachloroethylene	<0.5	<0.5	0.5
Dichlorobenzenes	<1.0	<1.0	1.0

Results — parts per billion of the analyzed compound

Population Average — The arithmetic mean derived exclusively from the U.S. population segment tested by Accu-Chem Laboratories.

IMPORTANT — Although these compounds are detected in the general population, they are foreign and serve no recognized beneficial function to the human body. In certain medical or legal instances serial testing may be advisable.

Statistical Data 5/24/91
Ave. variability factor calculated from [illegible] of the above [illegible] 20.7%
The variability factor will increase above 20.7% as results approach detection limit.

John L. Laseter, Ph.D.
Director of Laboratory

CLIENT COPY

APPENDIX C

MINI-MENTAL STATUS EXAM

Date: __/__/9_

#1	What is the year?	_____
#2	What is the season of the year?	_____
#3	What is the date?	_____
#4	What is the day of the week?	_____
#5	What is the month?	_____
#6	Can you tell me where we are? (for instance, what state are we in)?	_____
#7	What county are we in?	_____
#8	What city/town are we in ?	_____
#9	What floor of the building are we on?	_____
#10	What is the name or address of this place?	_____

I am going to name three objects. After I have said them, I want you to repeat them. Remember what they are because I am going to ask you to name them again in a few minutes.

Apple, Table, Penny

Please repeat the names for me.

#11	Apple	_____
#12	Table	_____
#13	Penny	_____

#14 Now I am going to give you a word and ask you to spell it forwards and backwards. The word is WORLD. First, can you spell it forwards? Now spell it backwards. _ _ _ _ _

What were the three objects I asked you to remember?

#15	Apple	_____
#16	Table	_____
#17	Penny	_____

#18	(Show wrist watch) What is this called?	_____
#19	(Show pencil) What is this called?	_____

#20 I would like you to repeat a phrase after me. (The phrase is) "NO IFS, AND'S OR BUT'S."

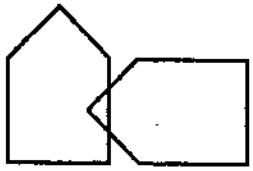
#21 Read the words on this page, then do what it says. (The paper reads) 'CLOSE YOUR EYES." I'm going to give you a piece of paper. When I do, take the paper in your right hand, fold the paper in half with both hands, and put the paper down on your lap.

#22	Right hand	_____
#23	Folds	_____
#24	In lap	_____

#25 Write any complete sentence on that piece of paper for me.

#26 Here is a drawing. Please copy the drawing on the same paper.

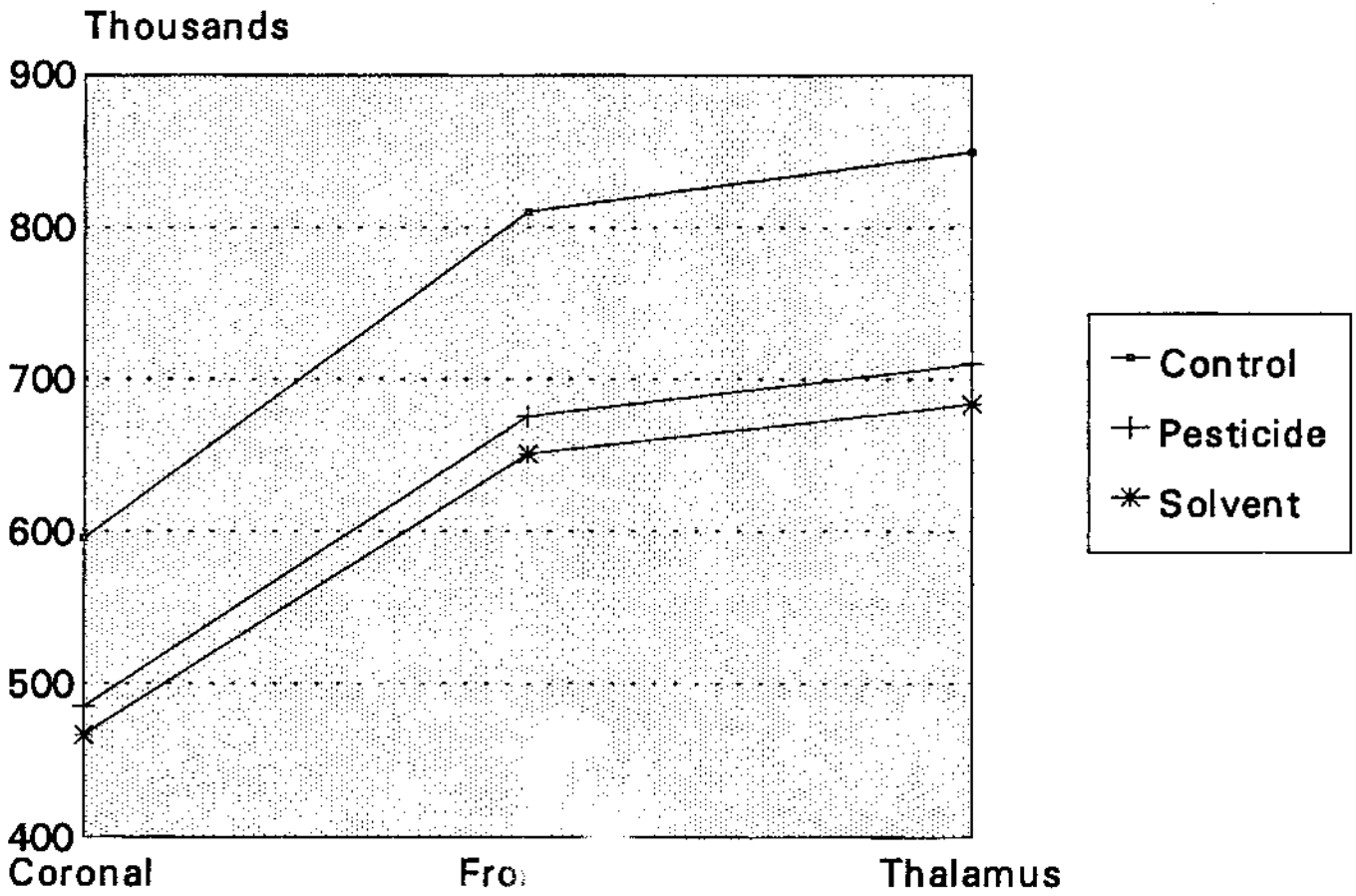
Close Your Eyes



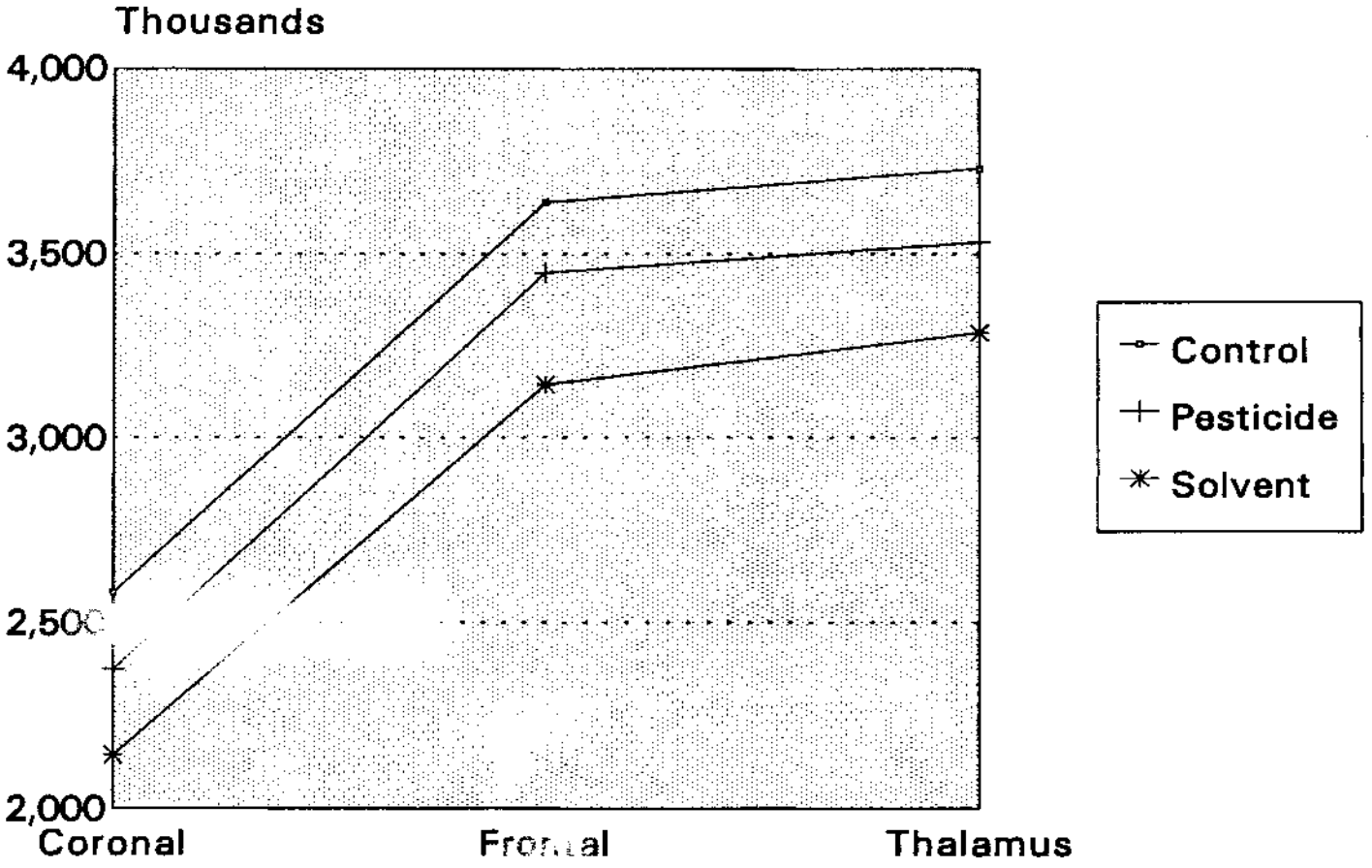
APPENDIX D

GRAPHS OF MEANS OF TRACER UPTAKE

Means of Flow Count in Tracer Uptake For Each Slice



Means of Function Count in Tracer Uptake For Each Slice



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