

DISEASE PROFILE

PERIPHERAL NEUROPATHY

I. DEFINITION

A. Dictionary

The term peripheral neuropathy includes any primary disorder of peripheral motor, sensory, and autonomic neurons. Neuropathies are classified as symmetrical generalized neuropathies, (or polyneuropathies as it is sometimes referred, including distal axonopathies, myelinopathies, and neuronopathies) focal neuropathies, and multifocal neuropathies.

B. Symptoms

The clinical hallmarks are muscle weakness, with or without atrophy, sensory change, autonomic manifestations, (i.e., changes in cardiac muscle, glands, or smooth muscle) or combinations of these. The motor weakness is sometimes associated with a loss in deep tendon reflexes. In other instances, fascicular twitching (i.e., spontaneous firing of individual bundles of muscle that can be observed through the overlying skin) occur. Some patients exhibit myotonia which is an increased muscular irritability and contractility with decreased power of relaxation resulting in muscle spasms. Sensory changes include sensory loss in the fingers and toes or tingling or pinprick sensations in the extremities followed by increasing sensory loss in the lower extremities, as well as in some instances pain and tenderness in muscles. Autonomic changes can include hyperactivity (i.e., decreased temperature) or reduced activity (i.e., warmth, swelling, discoloration, or shiny skin).

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C. Duration

Duration is variable lasting from a few days to several years depending on the type of neuropathy, its cause, and treatment.

D. Treatment

Drug treatment includes the use of cholinergic agents, steroids, carbamazepine, and DPH. Other treatments include: physical therapy with use of massage, exercise, and electrical stimulation. Orthoses are also used to prevent or correct contractures, or to stabilize joints in order to improve function.

E. Diagnostic Criteria

Because of the many different types of peripheral nerve disease, diagnostic criteria and protocol are highly variable. Medical history questionnaires are generally given along with clinical examinations which focus on muscle tone and reflex actions. More sophisticated techniques noted include computed tomography scans, electroencephalogram, lumbar puncture, skull and spine x-rays, and more specialized diagnostic procedures (i.e., myelography, electromyography, evoked potentials, and ultrasound) performed by a neurologist. Nerve conduction velocity studies are also used to assess subclinical observations, as well as to verify clinical changes.

II. EVIDENCE RELATING TO 2,4,5-T, TCDD OR 2,4-D EXPOSURE

A. Human Studies

1. Industrial Accidents

An explosion at a TCP Plant in Nitro, West Virginia in 1949 resulted in exposure of employees and clean-up crews to TCDD contaminated material. Severe pains in muscles of the upper and lower extremities were second to acneform lesions in order of relative frequency of clinically observed symptoms. A follow-up examination of workers three (3) years later revealed a general regression of symptoms.

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Some neurological complaints continued. No clinical explanation could be made based on the results of physical examinations. The exposure level of TCDD was not reported on in the study (1980, G).

An explosion at BASF chemical plant in West Germany in 1953 resulted in a total of 53 ill workers with seven (7) demonstrated cases of neurological organ damage. Toxic polyneuropathies were observed, including sensory and motor paresis of the lower arms and lower thighs, disorders of the ears, nose and taste organs, hyporeflexia (diminished reflexes), hyperalgesia (excessive sensitivity to pain), hypotonia of the musculature (diminished muscle tone), fatigue in the legs, and rheumatic complaints of the lower extremities (1973, L). Two (2) patients received pensions as a result of their peripheral nerve injuries. Each had a certification from medical specialists relative to the effect of dioxin as the cause (1976, J).

Workers exposed to TCDD as a result of an explosion at a 2,4,5-TCP production facility of the Coalite Company in England in 1968 resulted in no cases of peripheral nerve disease even though 79 cases of chloracne were reported. Levels of TCDD were not described (1973, M).

An explosion at a 2,4,5-Trichlorophenol plant in Seveso, Italy in 1976 resulted in a study of 470 people who, 18 - 20 days after the accident, had been evacuated from the most heavily contaminated area near the explosion. This area had an average TCDD level of 240 micrograms/square meter, a maximum level of 5,577 micrograms/square meter, and an unevaluable minimum level. Neurological symptoms identified included: paresthesia (abnormal sensation), hypesthesia (decreased sensitivity of the skin), generalized pain, and hyposthenia (weakness). Clinical signs included superficial and deep sensory impairment, muscular weakness, and tendon hyporeflexia (weakening of the reflexes), or areflexia (absence of reflexes). Ongoing studies have

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found that of the 470 subjects examined, there were twenty-two (22) cases with symptoms or clinical and electrophysiological signs of peripheral neuropathy, and twenty (20) cases with electrophysiological abnormalities. The prevalence rate of peripheral neuropathy among those with chloracne or abnormal enzyme hepatic levels was nearly three (3) times greater than those without these manifestations. However, no acute polyneuropathy was found during the study and the polyneuropathic cases found were not severe (1981, D). Other studies have questioned the validity of the findings of these ongoing studies. Reggiani has indicated that there is no correlation between the occurrence of chloracne and neurological findings (1980, F).

2. Occupational Exposure

The study of chronic industrial exposure of 73 male employees involved from 1964 to 1970 in the production of 2,4-Dichlorophenol, 2,4,5-Trichlorophenol and 2,4,5-T at a Newark, New Jersey plant of the Diamond Alkali Company revealed only two (2) cases of lower extremity weakness that could not be explained by other concomitant disease. However, the complaint of lower extremity weakness was not determined through the neurologic examination of any subject. Exposure levels to TCDD were not noted. However, TCDD levels in 2,4,5-Trichlorophenol ranged from 10 to 25 parts per million (1971, N).

A Czechoslovakian study looked at dioxin poisoning during 1965 to 1968 among workers involved in the production of 2,4,5-T. Of the 400 workers employed in the plant, 17 persons studied over a ten (10) year period have exhibited symptoms of nervous system focal damage, with a predominance of peripheral neuron lesions of the lower extremities. These peripheral nerve diseases were verified by electromyographic examinations. Results of repeated neurological examinations showed that during the initial three to four years of illness, the neurons of the

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lower extremities deteriorated. Neurological symptoms tended to stabilize or improve after four (4) years. Exposure concentrations for individuals were not described in the studies; however, it was noted that the 2,4,5-T produced commercially prior to 1965, contained 30 ppm of TCDD (1981, E).

A British study observed three (3) scientists who had minimal exposure to 2,3,7,8-TCDD. One of the scientists complained, of among other things, a decrease in muscular coordination. This symptom subsided over a period of about six (6) months. Injury claims including neurological disturbances such as lack of muscle control, abdominal pain, and blurred vision by the other scientists could not be attributed to dioxon exposure (1975, K).

Studies conducted on thirty-five (35) technicians responsible for examining samples coming from the TCDD polluted area of Seveso found significant differences in subclinical neurophysiological changes of the hands and toes as compared with the control group. It is unclear whether the neurophysiological data was a result of TCDD levels or exposure to other potentially neurotoxic agents such as the solvents used to extract the TCDD from the samples (1979, H).

A study of fifty-six (56) workers employed at some point from 1957 to 1979 in the manufacturer of 2,4,5-T and 2,4-D in a plant in Jacksonville, Arkansas, measured nerve conduction velocities of the median motor, median sensory, and sural nerves. An increased prevalence of slowed nerve conduction velocities was found among the workers when compared to control groups. Conduction velocities of the median motor and sural sensory nerves were significantly slower in the study group versus the control group. Slow sural sensory velocity was significantly correlated with duration of employment. The study did not identify clinically observable adverse health impacts beyond the slowed nerve conduction. The authors noted the importance

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of further study of the relationship of such signs of neurological changes to adverse effects in other body systems, either concomitant or delayed (1982, C).

3. Other

The accidental spraying of TCDD contaminated salvage oil in three (3) horse arenas in Missouri resulted in TCDD concentrations of about 30 ppm in the arena soil. Human health impacts studied have been limited to six (6) individuals exposed to the soil. - Aside from claims of headaches and polyarthralgia (pains in joints), the studies did not reveal any acute neurological impacts (1977, I).

Brandt reviewed the published cases of 2,4-D poisoning in humans as a result of agricultural and garden spraying, and a few suicide attempts. Peripheral neuropathies were verified in most of these instances, with some cases of incapacitating polyneuritis, and with recoveries ranging from three (3) months to over four (4) years (1971, O).

B. Animal Studies

1. Rodents

While most animal studies related to dioxin have focused on mortality or other signs of morbidity, Calder studied the effects of TCDD on peripheral nerve function in Wistar rats. Rats which survived the acute dosing of 35 micrograms per kilogram of TCDD were clinically assessed for evidence of gait abnormality, foot drop, impaired placing reaction, and toe spread reflex. The rats grew normally and showed no clinical evidence of polyneuropathy. Sections of sciatic and sural nerves were morphologically normal. The authors concluded that this animal study suggests that high dosage levels of TCDD are not toxic to the peripheral nerves. Chronic exposure to TCDD was not investigated (1982, B).

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Squibb, et al. in assessing the neurological toxicity of 2,4-D on Fischer-344 rats found that 2,4-D produced few signs of neurotoxicity in rats as measured by a battery of neurobehavioral screening tests. However, 2,4-D did produce a consistent increase in fore-and-hind limb grip strength during the five (5) week, twice a week dosing of 2,4-D representing approximately 5, 10, or 20% of the acute LD50 of 2,4-D (443 mg/kg) (1983, A).

III. ANALYSIS

While some studies do provide evidence linking TCDD exposure to peripheral neuropathies, the sufficiency of this evidence to meet the requisite standard of proof in court is questionable. Given the high number of recorded exposures to TCDD, the incidence of acute peripheral neuropathy is quite small. For example, the Seveso studies of a large population exposed to TCDD, while identifying some neurological symptoms and some electrophysiological abnormalities, found no acute polyneuropathy and the polyneuropathic cases found were not severe.

Causation evidence is also limited because the studies fail to establish a characteristic clinical picture for dioxin exposure and peripheral nerve disease. Symptoms appear highly variable. There is no evidence of a dose response relationship. These facts taken together with the limited number of animal studies and Calder's recent rat findings tend to cast some doubt as to the relationship of TCDD with peripheral neuropathy.

Evidence linking 2,4-D to peripheral neuropathy appears stronger. However, the majority of the human studies were associated with isolated instances of direct exposure from spraying, spills, and intentional ingestion. Aside from Singer's subclinical findings, there were no large scale studies showing wide spread peripheral nerve disease related to public and industrial exposures to 2,4-D. Furthermore, the

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animal studies while confirming some changes in neurological activity failed to demonstrate acute neurotoxicological effects of 2,4-D. As with TCDD, a dose response relationship has not been demonstrated making proof of low dose chronic exposure more difficult. Singer's findings may themselves be suspect because the study fails to demonstrate sufficient temperature controls before and during the testing.

IV. PRINCIPAL DOCUMENTS

- A. 1983. Neurobehavioral Assessment of 2,4-Dichlorophenoxyacetic Acid (2,4-D) in Rats.
Squibb, Robert E.; Tilson, Hugh A.; Mitchell, Clifford L.
Copy Attached
- B. 1982. Failure of Dioxin to Cause Polyneuropathy in Rats.
Calder, C.D.; Pollock, M.; Lovelace, R.E.
Copy Attached
- C. 1982. Nerve Conduction Velocity Studies of Workers Employed in the Manufacture of Phenoxy Herbicides.
Singer, Raymond; Moses, Marion; Valciukas, Jose; Lilis, Ruth; Selikoff, Irving
Copy Attached
- D. 1981. Relationship Between Clinical and Electrophysiological Findings and Indicators of Heavy Exposure to 2,3,7,8-Tetrachlorodibenzo-dioxin.
Filippini, Graziella; Bordo, Bianca; Crenna, Paola; Massetto, Nicoletta; Musicco, Massimo; Boeri, Renato
Carr Document No. — A-2626
Microfiche No. — A768 B09-C02
- E. 1981. The Development and Prognosis of Chronic Intoxication by Tetrachlorodibenzo-p-dioxin in Men.
Pazderova-Vejlupkova, Jana; Memcova, Marcela; Pickova, Jane; Jirasek, Lubor; Lukas, Edgar
Carr Document No. — A-2520
Microfiche No. — A639 C07-D02
- F. 1980. Localized Contamination with TCDD - Seveso, Missouri, and Other Areas.
Reggiani, G.; From Halogenated Biphenyls, Terphenyls, Naphthalenes, Dibenzodioxins and Related Products. Edited by Kimbrough, Renate D.
Copy Attached

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- G. 1980. The Mortality Experience of Workers Exposed to Tetrachlorodibenzodioxin in a Trichlorophenol Process Accident.
Zack, Judith A.; Suskind, Raymond R.
Carr Document No. — A-198
Microfiche No. — A78 C04-C08
- H. 1979. Neurological Monitoring of Workers Exposed to TCDD Preliminary Neurophysiological Results.
Gilioli, R.; Cotroneo, L.; Bulgheroni, C.; Genta, P.A.; Rota, E.; Cannatelli, P.; Ferrari, E.
Copy Attached
- I. 1977. Epidemiology and Pathology of a Tetrachlorodibenzodioxin Poisoning Episode.
Kimbrough, Renate D.; Carter, Coleman D.; Liddle, John A.; Cline, Richard E.; Phillips, Patrick E.
Carr Document No. — A-219
Microfiche No. — A82 B14-C10
- J. 1976. Follow-up Report on the Trichlorophenol-dioxin Accident at BASF AG on 13 November, 1953.
Thiess, A.M.; Goldmann, P.
Carr Document No. — A-887
Microfiche No. — A262 B13-C04
- K. 1975. Toxic Effects of 2,3,7,8-Tetrachlorodibenzo 1,4 Dioxin in Laboratory Workers.
Oliver, R.M.
Carr Document No. — B-286
Microfiche No. — B124 B01-B07
- L. 1973. Severe Acute Chloracne. A Mass Intoxication by 2,3,6,7-Tetrachlorobenzodioxin.
Goldmann, Paul J.
Carr Document No. — A-885
Microfiche No. — A262 A08-B04
- M. 1973. Chloracne From the Accidental Production of Tetrachlorodibenzodioxin.
May, George
Carr Document No. — B-277
Microfiche No. — B123 B-03-B12

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- N. 1971. A Health Survey of workers in a 2,4-D and 2,4,5-T Plant. With Special Attention to Chloracne, Porphyrin Cutanea Tarda, and Psychologic Parameters.

Poland, Alan P.; Smith, Donald; Metter, Gerald; Possick, Paul

Carr Document No. — B-958

Microfiche No. — B253 D03-E03

- O. 1971. Herbatox Poisoning, A Brief Review and a Report of a New Case.
Brandt, Mogens R.

Microfiche No. — G967 A02-A13

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VI. CONFOUNDERS

A. The following diseases are known to cause or manifest peripheral nervous system disorders:

1. Diabetes, Leukemia, Leprosy, Carcinomas, and Alcoholism.

B. The following industrial agents have been linked to neuropathies:

1. Acrylamide-catalytic polymerization of the monomer produces substances used as flocculators and grouting agents.

2. Carbon Disulfide - used in the vulcanization of rubber, as a phosphorus solvent in match manufacturing, and in the production of viscose rayon fibers and cellophane films.

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3. Dimethylaminopropionitrile (DMAPN) - used as a catalyst in polymerization reactions in the manufacture of polyurethane foams.

4. Ethylene Oxide - widely used in industry, especially in sterilizing heat-sensitive biomedical materials.

5. Methyl Bromide - used as a fumigant, fire extinguisher, refrigerant, and insecticide.

6. Hexacarbons - used as solvents and as minor components of gasoline, laquers, glues, and combustion products.

7. Organophosphorus Esters - used in insecticides, petroleum additives, and modifiers of plastics.

8. Triorthocresylphosphate (TOCP) - used as a softener in the plastics industry and as a heat-stable, high temperature lubricant.

9. Polychlorinated Biphenyls - used as plasticizers and in electrical insulation.

10. Trichlorethylene - used in dry cleaning, rubber production, and as a degreasing agent.

C. The following metals have been linked to neuropathies:

1. Lead - found largely in battery manufacturing, smelting of lead-containing ores, manufacture of pipe, sheet lead, solder, and lead alloys, use of industrial paints containing lead, and lead shot manufacture.

2. Arsenic - produced as a byproduct of copper and lead smelting processes. Used in pesticides, wood preservatives, glass manufacture, cattle and sheep dips, leather manufacture, paper dyes, and chemical warfare gases.

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3. Mercury - used as a fungicide.
4. Gold - used in the treatment of rheumatoid arthritis.
5. Platinum - used in cancer chemotherapy.
6. Thallium - used in insecticides, and in clinical use to treat ringworm.

D. The following drugs have linked to neuropathies: chloramphenicol, clioquinol, phenytoin, disulfiram, doxorubicin, ethambutol, isoniazid, misonidazole, nitrofurantoin perhexiline, thalidomide, glutethimide, and vinca alkaloids.

E. Dapsone, a drug used in Viet Nam for the treatment of malaria, has also been shown to induce peripheral neuropathy. In most patients, abnormalities have been entirely motor, with distal wasting and weakness. Mild paresthesias have also been noted. One patient also had depressed vibration sensation in the feet.

The reference for the preceding discussion on confounders including dapsone is: Peripheral Neuropathy, edited by Dyck, Peter J.; Thomas, P.K.; Lambert, Edward H.; Bunge, Richard; (W.B. Saunders Co. 1984). This book also contains primary references for the review articles.

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