Chlorpyrifos (Dursban) exposure and birth defects: report of 15 incidents, evaluation of 8 cases, theory of action, and medical and social aspects[a]

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Summary

Reported are adverse reproductive outcomes in 15 children, with a detailed analysis of eight children who demonstrate an unusual pattern of birth defects, affecting the brain, eyes, ears, nipples, palate, and genitalia, associated with *in utero* exposure to the household pesticide, chlorpyrifos (Dursban). The product is unique in that the active ingredient, chlorpyrifos, is both a chlorinated and an organophosphate chemical. Components of Dursban, including trichloropyridinol and sulfotepp, have potential dioxin contamination. The toxicology of each, and theories of action are presented. Theories of teratogenicity include direct neurotoxicity, possible DNA interaction, endocrine disruption, biochemical damage, and genetic interaction.

Key words: **chlorpyrifos, Dursban, trichloropyridinol, teratogenicity, hydrocephaly, mental retardation**

J.D. Sherman: Esposizione a clorpirifos (Dursban) e difetti alla nascita: resoconto di 15 casi incidenti, valutazione di 8 casi, meccanismo d'azione ed aspetti medici e sociali. Eur. J. Oncol., 4 (6), 653-659, 1999

Riassunto

Vengono riferiti gli effetti riproduttivi sfavorevoli in 15 bambini, con un'analisi dettagliata in 8 bambini che hanno mostrato un insolito pattern di difetti alla nascita, che interessavano l'encefalo, gli occhi, gli orecchi, i capezzoli, il palato ed i genitali, in seguito all'esposizione *in utero* al pesticida domestico clorpirifos (Dursban). Il prodotto è particolare in quanto l'ingrediente attivo, il clorpirifos, è un composto chimico clorato e nello stesso tempo organofosfato. Componenti del Dursban, compresi il tricloropiridinolo ed il sulfotepp, hanno una potenziale contaminazione da diossina. Vengono presentati la tossicologia ed i possibili meccanismi d'azione di ciascuno di essi. Le teorie sulla teratogenicità comprendono la neurotossicità diretta, la possibile interazione con il DNA, disturbi endocrini, danni biochimici ed interazioni genetiche.

Parole chiave: **clorpirifos, Dursban, tricloropiridinolo, teratogenicità, idrocefalo, ritardo mentale**

Introduction

A number of papers linking pesticide exposure and birth defects in children have been reported (Czeizel, 1996). Garry *et al.* (1996) found a significant excess of all anomalies in children born to private pesticide applicators, varying by crop-growing region. A pattern of birth defects and alteration of the sex ratio, related to seasonal pesticide use, emerged in crop-growing western Minnesota where there is a high use of fungicides and chlorophenoxy herbicides. In that same state, severe birth defects were found in frogs at more than 100 sites, in 54 of 87 counties (Souder, 1996). Sharing common exposures, these findings in humans and animals further link adverse developmental effects (Colborn and Clement, 1992). The special susceptibility of children to pesticides is well-documented, as is the failure of science and law to adequately protect children (National Research Council, 1993; Wargo, 1996). The type or pattern of embryonic anomaly varies according to the toxic agent(s) and timing of exposure during pregnancy. The rapidly

[a] The author has no financial interest in the cases described herein. The author was paid for her time to examine six of the children as well as for her time to review the medical records of one child who died. The author has not been compensated for her time to review the documents, supplied as a courtesy, for two of the children, nor for her time and costs to research and write this paper.

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developing neurological organs of the embryo/foetus are particularly vulnerable to damage by chemicals designed to be neurotoxic in pesticidal action.

Fat-solubility of a chemical is a critical factor in production of adverse effects, including endocrine, reproductive, neurotoxic, immunotoxic, and oncogenic effects (Sherman, 1994). In addition to respiratory and oral routes, fat-soluble chemicals are absorbable through the intact skin, by-pass the hepatic circulation, have a prolonged residence-time (half-life) within lipid stores of the body; and pass the placental barrier.

With few exceptions, links between exposure to chemicals (industrial or pharmaceutical) and birth defects or cancer have been demonstrated on the basis of early case reports by alert clinicians. As early as 1933, the developers of diethylstilbestrol (DES) cautioned as to the carcinogenicity of such products (Cook, Dodds and Hewett, 1933). DES use during pregnancy was curtailed on the basis of seven cases of cancer of the vagina in young women, but not until 1970 (Herlstand and Scully, 1970; Herbst, Ulfeder and Proskanzer, 1971). Two plant physicians from Goodrich alerted the world as to the consequences of vinyl chloride exposure when they reported three cases of liver cancer that had occurred in the industry (Creech and Johnson, 1974).

Few epidemiological studies for teratogenicity have been carried out on specific chemicals, and of these, including thalidomide, data were not collected until the foeto-toxicity of the product had been under question. Foetal damage has been documented for a number of industrial and pesticidal chemicals. Subtle changes in intelligence, memory, attention, and reading ability has been found in children exposed *in utero* to PCB-contaminated fish consumed by their mothers (Jacobson and Jacobson, 1996). Two decades ago, embryotoxicity was found in animals and humans exposed to Agent Orange (composed of 2,4-dichlorophenoxyacetic acid) and 2,4,5-T trichlorophenoxyacetic acid (2,4-D and 2,4,5-T). Adverse effects included abortion, stillbirths, and congenital malformations (Laporte, 1977).

Following the Icmesa chemical plant explosion in Seveso, Italy, where trichlorophenol was manufactured, a number of adverse effects were reported (Laporte, 1978). Exposure to dioxin (specifically TCDD) resulted in a decrease in male children (26 males vs 48 females) born over a period of 8 years (Mocarelli *et al.*, 1996). A similar decline in male births in Denmark has been reported, postulating embryotoxicity from chemicals, including the nematocide dibromochloropropane (DBCP) (Moller, 1996).

Despite a 1977 US EPA issuance of a rebuttable presumption against registration of Benomyl because of teratogenicity (Kavlock *et al.*, 1982), reduction in sperm activity, interference with spindle fibre formation and chromosome function (US EPA, 1977), and hydrocephalus in test animals (Ellis *et al.*, 1988), use has continued, culminating in a jury award against the manufacturer DuPont, after a pregnant woman, sprayed with Benomyl in 1989, gave birth to a boy without eyes (Castillo vs DuPont, 1989).

The various Dursban products contain, as the active ingredient, chlorpyrifos, which is both an organochlorine and an organophosphate pesticide [b]. Since publication of the first four cases of Dursban-associated birth defects (Sherman, 1995a, 1996) four additional children have been identified with a similar pattern of defects and a history of *in utero* exposure to Dursban. The anomalous defects in eight children are shown in Table 1.

Methodology

Thorough investigations were done to rule out potential causes of birth defects in these children. Parental interviews and medical records were reviewed for eight children, and physical examinations were conducted on six. One child has died. Other causes of birth defects were explored, including family history, maternal smoking and alcohol consumption, infections, chromosomal abnormalities, and the mother's exposure to other chemicals. All children had a history of Dursban exposure during in *utero* life. Three children had chemical exposures in addition to Dursban: one to a solvent-containing product; one to cypermethrin; and one to diazinon and Bengal Roach and Ant Spray [c].

Clinical findings

Anomalous defects in eight children are shown in Table 1.

All of the boys in this report have undescended testicles, three have microphallus, and one of four girls has a fused labia. Chlorpyrifos was negative for oestrogenicity in the E-SCREEN and assay systems (Arnold *et al.*, 1996; Soto, personal communication). A component of the product having anti-androgen effect is postulated to be operative (Guillette, personal communication, 1996), however the component and the mechanism of action is unknown at this time.

All of the children are intellectually retarded, all but one requiring feeding, diapering, and constant monitoring.

Chromosomal studies were normal in each child, none of the mothers smoked, none had significant medication or alcohol use. Each family had other children, not affected, and born at a time when Dursban was not used. The data are presented in Table 2.

All of the pregnant women and their foetuses were exposed beginning in the first trimester of pregnancy. Due to the persistence of Dursban, seven children were exposed essentially throughout intrauterine life, beginning in the first trimester of the mother's pregnancy. This prolonged exposure is reflected in the severity of their defects. One exception is case 4, with the shortest exposure time of the group who although severely physically compromised, has the most functional ability.

Monitoring data for pesticide levels, either at the time of pesticide application or at the time of birth was simply not done. It was not until significant time had elapsed, many different examiners had evaluated the children, and known causes of birth defects had been eliminated that pesticide exposure was taken under consideration.

Unfortunately, consideration of Dursban as a factor was impeded

[b] Marketed by DowAgro, a subsidiary of Dow Chemical Co.; previously marketed by DowElanco, a coordinated effort between Dow Chemical Co. and the pharmaceutical corporation Eli Lilly, and sold under a variety of names including the Dursban series, Lentrek, Lorsban, Empire, Killmaster II, Duratrol, Whitmore, Demon, Equity and Others

[c] Bengal spray contains 3-phenoxybenzyl- (1RS, 3 RS; 1RS, 3SR)-2,2-dimethyl-3-(2-methylprop-1-enyl) cyclopropanecarboxylate 1.5%; d-trans-chrysanthemum monocarboxylic acid ester of dl-2-allyl-4-hydroxy-3-methyl-2-cyclopenten-1-one 0.1%; piperonyl butoxide, technical 0.4%; and 98% unknown components listed as "inert ingredients".

Table 1 - Birth defects in children exposed *in utero* to Dursban [a]

	Child N.							
Sex	1 F	2 M	3 M	4 F	5 F	6 M	7 F	8 M
Brain defects								
Structural deformities	+	+	+	+	+	+	+	+
Ventricular	+	+	+	+	+	+	+	–
Microcephaly	+	+	+	–	+	+	–	–
Hydrocephaly	+	+	0	+	+	–	+	–
Atrophy of brain	–	+	+	–	+	+	+	–
Abnormality type	CC	CC	SP			DM	CC	CC
Eye defects								
Structural	Mi	Mi/C	Mi	Cl			+	+
Blind	+	OT	+	0	+	LO	0	LO
Cataract	+	0	+	0	+	+	0	0
Facial								
Palate abnormality	+	+	+	+Cp	+	+	+	+
Cleft lip	0	0	0	+	0	0	CT	+
Tooth abnormality	+	0	+	+	+	–	+	+
Nose abnormality	+	0	0	+	SM	SM	+	+
External ear	+	+	0	+D	0	0	+	+
Other	7N	As	As					RP
Heart	–	H1	H2	–	U	+	–	ASD
Genital								
Abnormal external	+	+	+	0	+	+	U	+
Specific abnormality	F	U	U/P			U/P		U/M
Other								
Mental retardation	+	+	+	N	+	+	+	+
Nipples wide-spread	+	0	+	+	+	+	+	+
Foot abnormalities	+	+	+	0			+	–
Hypotonia		+	+	–		+	+	+
Growth retardation	+	+	+	+	+	+	–	+

[a] N = Normal; 0 = Defect not present; + = Defect present; Cp = Cleft palate; CC = Corpus callosum; SP = Septum pellicudum; Mi = Micro-ophthalmia, C = Cyst of eye; Cl = Cleft in eye; OT = Optic tracts abnormal; D = Totally deaf; F = Fused labia; U = Undescended testes; P = Micro-phallus; DM = Demyelinization; CT = Cleft tongue; 7N = Seventh cranial nerve palsy; AS = Asymmetry; H1 = Atrial-septal defect and pulmonary stenosis; H2 = Right aortic arc; – = Defect not apparent, determination delayed until growth is achieved, and/or surgical and autopsy findings

Table 2 - Review of medical history and chemical exposures [a]

	Child N.							
Findings	1	2	3	4	5	6	7	8
Chromosome studies	N	N	N	N	N	N	N	N
Maternal smoking hx	no	no	no	no	no	no	no	no
Maternal alcohol use	no	no	no	A	no	no	no	no
Infections during PGcy	no	+	no	no	no	no	no	no
PGcy medication use	T	S	T	0	Ty	Ty	Pr	0
Family history of birth defects								
Child's mother	0	0	0	0	0	0	0/#	0
Child's father	0	0	0	0	0	0	0/@	0
Matern. grandmother	0	0	0	0	0	0	0	0
Matern. grandfather	U	0	U	0	0	0	0	0
Patern. grandmother	0	0	0	0	0	0	0	0
Patern. grandfather	0	0	0	0	0	0	0	0
Birth defects in other siblings	0	0	0	0	0	0	0	0
Other chemical exposures during pregnancy	0	C	0	F	0	0	Cy	D/B
Dursban product used (+ where specific Dursban product is unknown)	LO	TC	LO	LO	+	+	270	Sp

[a] N = Normal; 0 = None; A = "A couple of sips of wine one time during pregnancy"; T = Occasional Tylenol; S = Occasional Sudafed, amoxicillin -1 course of treatment; C = Home previously treated with chlordane; F = Firefog; U = Unknown; Cy = Cypermethrin; # = Craniostosis in brother's child; @ = Learning disability in seizure in past; Ty = "Maybe a Tylenol"; Pr = Progesterone; Sp = Spectricide; D = Diazinon; B = Bengal spray

by a significant delay in Dursban reports sent to the US EPA (4), as required by the Federal Fungicide, Insecticide and Rodenticide (FIFRA) law (1978) wherein the registrant must report all adverse pesticide effects to the US EPA within 30 days.

Following a television news programme that documented adverse reactions following exposure to Dursban, the manufacturer Dow-Elanco (now DowAgro Sciences) reported the following 13 adverse reproductive cases (5):

"DERBI" No. 9920 (exposure date: 6-94; report date: 11-03-94). A premature birth following home application of Dursban TC and Diazinon.

"DERBI" No. 23154 (exposure date 5-88; report date: 10-12-94). Delayed peripheral neuropathy in a boy resulting in quadriplegia and respiratory dependency following home application of Dursban LO and 2E, diazinon, safrotin and pyrethroid pesticides.

"DERBI" No. 23178 (exposure date: 8-87; report date: 10-12-94). Brother and sister, "who allegedly are quadriplegic, blind, have malformed genitalia, and have other physical and mental impairments." Exposure to Dursban LO and Dursban 6R.

"DERBI" No. 23194 (exposure date: 8-91; report date: 11-02-94). A girl, born prematurely with a sacrococcygeal teratoma, died following surgery. Exposure was to Dursban LO and Dursban R.

"DERBI" No. 23296 (exposure date: 2-91; report date: 11-02-94). Child born with "abnormal ventricles of the brain, abnormal corpus callosum, facial deformities including ears and eyes and paralysis of left side of face." Exposure was to Dursban LO and Firefog 404.

"DERBI" No. 23397 (exposure date: 9-88; report date: 11-02-94). Miscarriage 16 days after exposure to Dursban TC.

"DERBI" No. 23436 (exposure date: 9-87; report date: 11-02-94). A boy born with "cystic mass of the right eye, coloboma of the right eye, absent testes, poor muscle tone, seizures, microopthalmia" following use of Dursban TC.

"DERBI" No. 23575 (exposure date: 6-93; report date: 11-02-94). Miscarriages in three women exposed in a nursing home to Dursban.

"DERBI" No. 23577 (exposure date: 10-94; report date 11-02-94). Miscarriage following Dursban.

Reported after November, 1994 was "DERBI" No. 28735 (11-02-95). Birth defects in a child exposed during "an adult females *(sic)* pregnancy" to Whitmore 270 (containing Dursban), and Demon WP, a cypermethrin product.

Veterinary cases reported by Dow included deformed puppies born to a German shepherd breed dog, owned by a man and woman who developed classic organophosphate pesticide symptoms following application of Dursban 2E and Dursban LO to their home ["DERBI" No. 23415, (11-02-94)]. Also reported to DowElanco were deformed kittens born to a cat owned by an elderly couple who developed adverse reactions to Dursban.

Four children, reported by Dow to EPA are included in this serie of eight cases. This leaves a combined total of 15 childre with either birth defects or other adverse outcome, includin death.

Review of published and unpublished reports

The precise mechanism or mechanisms of Dursban teratogenicity remain unknown. Under considered are a combination of factors including the following: direct action of chlorpyrifos, o trichloropyridinol, and/or of chlorpyrifos-oxon; direct neurotoxicity; DNA interaction; endocrine disruption; sulfotepp contamination; possible dioxin contamination; biochemical-genetic interaction; or other unknown factors.

Dursban, like other pesticides, is not a single chemical product, but contains a number of impurities formed during manufacture and storage, as well as intentionally added chemicals such as solvents, wetting agents, etc. (6) (Dietz *et al.*, 1983).

Fig. 1 shows the chemical structure of chlorpyrifos, and its breakdown products, chlorpyrifos -oxon, and trichloropyridinol. Included in the figure are the structures of trichlorophenol and 2,4,5-T (2,4,5-trichlorophenoxy acetic acid), a component of Agent Orange, linked to birth defects (Agent Orange Scientific Task Force, 1990).

Trichloropyridinol (TCP), the feed-stock for the production of chlorpyrifos, also a contaminant in the product, and a metabolic break-down product has been determined to cause central nervous system anomalies (hydrocephaly and dilated brain ventricles), and other anomalies (cleft palate, skull and vertebral abnormalities) in the same fetus, at doses nontoxic to the mother (Hanley, Zielke and Lomax, 1987a; Dow Chemical, 1991), similar to those defects seen in affected children.

TCP administered to rats via gavage at doses of 0, 50, 100 and 150 mg/kg/day on days 6-15 of gestation, produced anophthalmia and dilated cerebral ventricles at the 100 mg/kg level; face and jaw abnormalities at the 50 and 150 mg/kg levels; and skull ab-

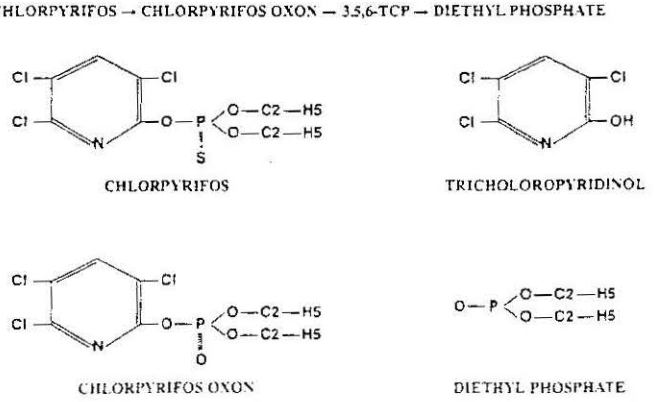

Fig. 1 - Metabolism of chlorpyrifos.

(4) Pursuant to a Consent Agreement, DowElanco agreed to pay a civil penalty of $832,000 for the delay.

(5) Report are available from US EPA under a Freedom of Information Request. Cases were reported under a numbering system named "DERBI" (Dow Elanco Research Business Index). Noted are the "DERBI" number, date of original complaint as given in corportate records, and date when reported to EPA.

(6) U. S. Patents Nos. 4,380,537, Apr. 19, 1983; 4, 388,297, June 14, 1983; 4,460,572, June 17, 1984; 4,631,301, Dec. 23, 1986; 4,810,793, Mar. 7, 1989; 4,849,415, July, 18, 1989; 4,888,174, Dec. 19, 1989; 5,079,238, Jan. 7, 1992.

normalities at the 150 mg/kg level (Hanley, Zielke and Lomax, 1987a).

In the chick embryo assay, chlorpyrifos metabolites (pyridyl phosphate and pyridinol) were more toxic than the parent compound, resulting in embryo death at lower doses (Muscarella, Keown and Bloom, 1984). In tissue culture assay, neurological damage resulted from exposure to chlorpyrifos (Cosenza and Bidanset, 1995)

The teratogenicity of TCP, based upon the Dow study of 1987 was not reported to the EPA until 1992 (Wright, 1992). TCP is used to manufacture the pesticide chlorpyrifos and as such comes under the regulation of Section 8(e) of the US Toxic Substances Control Act which requires "any person who manufactures, processes, or distributes in commerce a chemical substance or mixture, or who obtains information which reasonably supports the conclusion that such substance or mixture presents a substantial risk of injury to health or the environment, shall immediately inform the Administrator of such information, unless such person has actual knowledge that the Administrator has been adequately informed of such information."

Exposure and uptake are dependent upon the environmental half-life (T/2) of a chemical. In the case of chlorpyrifos, the pesticidal ingredient in Dursban, the T/2 claimed by the manufacturer ranges from 68 ± 13 days (Dow Chemical, 1983) to 18 years (Dow Chemical, 1985). US EPA data indicate soil persistence for 279 days (USEPA, 1984). Measurements taken over a four year period after chlorpyrifos application for termite control revealed ambient air levels up to five times greater than at the time of application (Leidy, Wrigth and Dupree, 1993). Volatilization and deposition upon environmental surfaces, which act as reservoirs, results in dermal exposure to both children and adults (Gurunathan *et al.*, 1998). Thus chemicals remain biologically available long after initial application.

Throughout intrauterine life, the developing foetus undergoes rapid cell growth, self-programmed cell death (apoptosis), and cell rearrangement, all time- and space-dependent. Interference with any of these processes results in abnormalities of subsequent growth and development.

As yet unknown mechanisms may be involved, linked to basic cell genetic and metabolic processes. Chlorpyrifos can affect cell development via altering the activity of the adenyl cyclase signaling cascade, a major point for regulation of cell differentiation. "The effects are not restricted to cholinergic targets, nor even to the central nervous system. Hence disruption of cell development by chlorpyrifos is likely to be more widespread than previously thought" (Song *et al.*, 1997). The metabolic product, chlorpyrifos-oxon, binds directly to muscarinic receptors and inhibits cyclic-AMP in the rat brain striatum (Huff *et al.*, 1994). Of the twenty-eight Dursban genetic toxicity tests reported in the EPA data base in 1996, nineteen are negative for gene mutation, three are positive for DNA damage, one is positive for aneuploidy, and two are positive for micronucleus disruption (Jackson, Start and Waters, 1996). An epidemiological study of insecticide and fumigant applicators demonstrated breaks in chromosomes of tumour suppression genes and apoptosis alterations (Garry *et al.*, 1996).

Designed to be neurotoxic in action, chlorpyrifos, the active organophosphate ingredient, may result in direct adverse effects upon the fetal central nervous system (Chandra and Pope, 1996). Chlorpyrifos, administered subcutaneously to day old rats at 2 mg/kg showed "significant DNA synthesis in all brain regions within 4 hours of treatment" and "inhibition of protein synthesis throughout the brain." The "results indicate that low doses of chlorpyrifos target the developing brain during the critical period in which cell division is occurring, effects which may produce eventual cellular, synaptic, and behavioural aberration after repeated or prolonged subtoxic exposures"(Whitney, Seidler and Slotkin, 1995).

Assays of 96.8% "feed-grade" chlorpyrifos on fetal and embryonal development showed reversal of the male:female ratio in mice at the 1.0 and 10.0 mg/kg dose groups; encephalopathy and sternebrae abnormalities in the 0.1 mg/kg group; and skull and sternebrae malformations in the 25 mg/kg group. Significantly increased major malformations were produced at the 1.0 mg/kg dose (Deacon *et al.*, 1979).

The same Dow researchers, employing lower doses, again produced reversal of the male:female ratio; significant skull abnormalities in the 1.0 and 10 mg/kg groups, despite the fact that "four litters of the mice at the 1 mg/kg dose level, and five litters of mice at the 10 mg/kg dose level were not examined for bones of the skull." Major malformations, including cleft palate in 4%, irregular pattern of ossification in 11% were produced at the 1 mg/kg level. "Among litters of mice given 1 mg/kg of chlorpyrifos, the incidence of exencephaly was significantly increased over control values." Exencephaly was produced in one fetus at the 0.1 mg/kg level (Deacon *et al.*, 1979).

A 1971 three generation reproduction study of Dursban by Dow showed hydrocephalus at doses of 0.1 and 0.03 mg/kg/day administered to the rats in their feed. Also produced were unilateral testicular hypoplasia, sternebrae, kidney and tail abnormalities (Thompson, Gerbig and Warner, 1971a).

A teratology study of Dursban, administered by gavage in corn oil at 0, 0.1, 0.3 and 1.0 mg/kg/day, reported a total of 1075 fetuses, of which 238 (22%) were examined, and of these 84 (8%) were evaluated for soft tissue abnormalities. Tables 9 and 10 of the Dow document indicate that no animals in the 0.1 and 0,3 mg/kg level were examined. At the 1.0 mg/kg dose level there were 79 sternebrae abnormalities (vs 45 in controls) and 95 urogenital abnormalities (vs 46 in controls.) (Thompson, Gerbig and Warner, 1971b).

A question of possible dioxin contamination of Dursban contributing to teratogenicity remains unanswered. In response to an US EPA-Call-in for data, Dow Chemical Co. submitted information concerning synthesis of a single dioxino-dipyridine analog (Birking, 1990); and five batch analyses for that single analog; and no other analogs. No raw data were included and results were claimed confidential (Bernan and Coborn, 1992).

Sulfotepp contamination of Dursban has been raised as a possible contributing factor. While no data are available as to specific testing of sulfotepp for teratogenicity, both Dursban (Allender and Keegan, 1991) and Diazinon (Turle and Levae, 1987) have been found to contain sulfotepp, with levels ranging from 1.5 to 6.5 mg/ml in Dursban.

Hormonal synergism has been demonstrated with combinations of pesticides and augmented estrogenicity with combinations not found to be estrogenic alone. Combinations of two chemicals having weak estrogenic activity alone, such as dieldrin, endosulfan, or toxaphene, were 1000 times more potent in combination (Colborn, vom Sall and Soto, 1993; Soto, Chung and Sonnenshein, 1994; Arnold *et al.*, 1996).

Discussion

Birth anomalies, as with cancer, usually occur one-at-a-time, often seen in isolation by the treating physician who may or may not ask "why?" Only recently has the US created a centralized data bank for collection of information on birth defects at the Centers for Disease Control. Despite birth defects registries, such as that of California, no US public health agency actually investigates each deformed child for potential teratogenic exposure(s).

The challenge to identify agents causing harm to children and the unborn has never been more important. The social and economic burdens imposed upon the families of deformed and impaired children is a significant public health problem. The societal burdens include loss of productivity for the affected children and their care-giving parents, and provisions for special medical, social and educational needs.

The following has been proposed to satisfy proof of human teratogenicity. The author notes: "Items 1-3 or 1,3 and 4 are essential criteria. Items 5-7 are helpful but not essential" (Shepard, 1994).

1. Proven exposure to agent at critical time(s) in prenatal development.
2. Consistent findings in epidemiological studies of high quality.
3. Careful delineation of clinical cases. A specific defect of syndrome, if present, is very helpful.
4. Rare environmental exposure associated with rare defect. Probably three or more cases.
5. Teratogenicity in experimental animals important but not essential.
6. The association should make biological sense.
7. Proof in an experimental system that the agent acts in an unaltered state. "Important information for prevention".

Foremost in medicine and law is the precept that purposeful exposure of pregnant women to toxic agents is unethical, thus prospective epidemiological studies cannot and ought not be done.

Thus, the cases discovered to date satisfy all criteria except the second. Unfortunately pregnant women have become exposed to a product demonstrated to have teratogenic effects, and a number of their progeny show a concordant pattern of birth defects. It is in this context that case reports are of critical importance. How many more cases that will be recognized and reported is simply unknown.

It follows that the type of neurological damage reflects timing of exposure and the state of growth and function of the persons' body, and can vary from death of the embryo/foetus; structural and functional abnormalities during foetal and newborn life; to functional abnormalities in preschool children (Guillette *et al.*, 1998). Exposure occurring in early childhood has resulted in profound neurological damage, expressed as quadriplegia. Children have developed peripheral neuropathy and the onset of hyperkinesis following exposure, and adults have developed both peripheral neuropathy and organic central nervous system damage (Sherman, 1995).

Public concern has been raised about the seeming rise in learning and behavioural problems in children, concomitant with increased indoor use of pesticides (Colborn, Dumanoski and Myers, 1996), especially organophosphates, designed intentionally to be neurotoxic. To date, few children with learning disabilities have had thorough clinical or epidemiological investigations into pre-natal and childhood exposure to pesticides and other toxic chemicals to determine the cause(s) of this wide-spread public health problem.

Conclusion and recommendations

Adverse reproductive effects from Dursban have been reported for 15 children; detailed evaluation is presented for eight children exposed *in utero*; the concordant pattern of defects is unusual and uncommon; positive teratogenic effects have been produced with chlorpyrifos, chlorpyrifos-oxon, trichloropyridinol and Dursban (the commercial product) in animals and other assay systems; biological mechanisms demonstrate interference with DNA and protein synthesis; chlorpyrifos inhibits cholinesterase; interferes with adenyl cyclase cascade; and is directly neurotoxic.

The precautionary principle requires that when risks become known, even hypothetical risks, action should be taken to avoid exposure to those risks. The concept of responsible public health, ethics and morality dictate caution and prevention. Given worldwide use of this product aggressive case-finding is needed worldwide, as is cautionary warning for women of child-bearing age

The physical and emotional stresses upon the parents and siblings of the children are incalculable. Given the enormous cost of caring for affected children (running in excess of $500,000 in direct costs) the economic burdens on society are enormous: special schooling, special equipment, extensive and costly medical care, and saddest of all, loss of human potential.

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