



Building a Database of Developmental Neurotoxicants: Evidence from Human and Animal Studies

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Introduction

EPA's program for the screening and prioritization of chemicals for developmental neurotoxicity makes it essential to assemble a list of chemicals that are toxic to the developing mammalian nervous system. Listed chemicals will be used to evaluate the sensitivity, reliability, and predictive power of alternative developmental neurotoxicity assays. To establish this list, a literature review was conducted for over 400 compounds that have been suggested to be developmental neurotoxicants, neurotoxicants, or developmental toxicants. Compounds were assigned one of three groups based on the strength of the evidence for developmental neurotoxicity:

- (1) **no evidence**: either there were no reports that met our criteria for evidence, or there were reports which showed no developmental neurotoxicity;
 - (2) **minimal evidence**: one report only or multiple reports from only one laboratory; or
 - (3) **substantial evidence**: reports from more than one laboratory.
- The chemicals in the latter group will be especially useful for vetting protocols that have been proposed as screens for developmental neurotoxicity.

This presentation has been reviewed by the National Health and Environmental Effects Research Laboratory and approved. Approval does not signify that the contents reflect the views of the Agency.

Approach

Collect lists of putative DNT chemicals (n≈400)

- Consult EPA RED* documents
- Consult Literature

- Assess Documentation
- Discuss Level of DNT Evidence
- Prepare Manuscript

Each chemical was assigned to one of three categories:

1. No available evidence existed: exclude from manuscript.
2. Minimal evidence existed: put in table in manuscript.
3. Substantial evidence existed: write a descriptive paragraph for manuscript.

Evidence: Criteria for Assessment and Endpoints

- a) We included only mammalian studies.
 - no *in vitro* studies were included.
- b) We included only studies with the pure chemical (or reasonably so).
 - no mixture studies were included.
 - no human studies were included wherein there was exposure to more than one compound.
 - no formulations were included.
- c) We included only studies where the exposure took place during pregnancy or during the period before weaning.
- d) We included only studies in which the administered dose was below 5 grams/kg.
- e) Where knowledge was available, we considered only studies where the administered dose would not be lethal to the offspring.
- f) We did not include any case reports.
- g) In studies where the chemical was administered during gestation, to the extent possible, we looked for a litter-based statistical design.
- h) If **only** acute pharmacological effects were reported (either during dosing or shortly thereafter), we did not include that study.

Endpoints assessed included, but were not limited to:

- | | |
|--|---|
| <input type="checkbox"/> Head Circumference | <input type="checkbox"/> Grip Strength |
| <input type="checkbox"/> Brain Weight | <input type="checkbox"/> Negative Geotaxis |
| <input type="checkbox"/> Exencephaly | <input type="checkbox"/> Startle Response |
| <input type="checkbox"/> Brain Morphology | <input type="checkbox"/> Righting Reflex |
| <input type="checkbox"/> Motor Activity | <input type="checkbox"/> Neurochemical Levels |
| <input type="checkbox"/> Learning and Memory | <input type="checkbox"/> Receptor Affinity/Number |

Chemicals with Minimal Evidence of Developmental Neurotoxicity (n≈100)

1,1,1-Trichloroethane	Diaminotoluene (2,5-)	Lidocaine
Abamectin	Dichloromethane (methylene chloride)	Malathion
Acephate	Dichlorvos (DDVP)	Mancozeb
Acetaminophen	Dicrotophos	Maytansine
ActinomycinD	Difluoromethylornithine	Methamidophos
Amicarbazone (MKH 3586)	Dimethoate	Methyl Ethyl Ketone
Astemizole	Dinoseb	MNDA
Atravastatin	Diphenhydramine	Molinate
Atrazine	Disulfoton	Naled
Azinphos methyl	Emamectin	n-Hexane
BAS 510 (Boscalid)	Endosulphan	Nickel carbonyl
BAS 670H	Endrin	Perchlorate
Bifenthrin	EPTC (S-Ethyl dipropylthiocarbamate)	Phorate (BAS 225 I)
Bismuth Ribromophenate	Ergotamine	Picrotoxin
Brominated veg oil	Ethoxyethanol (2-)	Primidone
Busulfan	Ethylene dibromide	Profenofos
Carbofuran	Ethylene oxide	Prothioconazole
Carbon disulfide	Etofenprox	Selenium compounds
Chlordane	Fenamiphos	Sinvastatin
Chlordimeform	Fenitrothion	Spirodiclofen
Chlorfenapyr	Fenvalerate	Succinimide
Chlorite, sodium	FK 33-824 (Synthetic enkephalin)	Terbufos
CI-943 (Antipsychotic)	Flufenacet (thiaflumide)	tert-Butylhydroquinone, 2-
Clodinafop-propargyl	Formaldehyde	Tetrachloroethylene
Clothianidin	Glufosinate ammonium	Tetracycline
Coumaphos	Glyphosate trimesium	Thiamethoxam
Cyfluthrin	Hexachloroplatinate (Na)	Tribufos (DEF)
Cyhalothrin	Imidacloprid	Triethylene glycol dimethyl ether
Cymoxanil	Ivermectin	Trimethadone
Danazol	Lasfoxfifene	Triphenyl phosphite
DDT	Levo-alpha-acetylmethadol	VM-26 (Teniposide)
Dextromoramide		VP-16-213 (Etoposide)

Chemicals with Substantial Evidence of Developmental Neurotoxicity (n≈100)

2-Ethoxyethyl Acetate	Diazepam	Naltrexone
Acibenzolar-S-methyl	Cytosine Arabinoside	Nicotine
Acrylamide	DEET	Methoxyethanol, 2-
Aldicarb	Deitamehrin	Methylazoxymethano
Allethrin	Diazinon	Methylmercury
Aluminum (cl or lactate)	Dieldrin	Ozone
Amino-nicotinamide(6-)	Diethylstilbestrol	Paraquat
Aminopterin	Diphenylhydantoin	Parathion (ethyl)
Amphetamine(d-)	Epidermal Growth Factor	PBDEs
Arsenic	Ethanol	PCBs (generic)
Aspartame	Ethylene thiourea	Penicillamine
Azacytidine(5-)	Flourouracil(5-)	Permethrin
Benomyl	Fluazinam	Phenylacetate
Benzene	Fluoride	Phenylalanine (d,l)
Bioallethrin	Griseofulvin	Phthalate, di-(2-ethylhexyl)
Bis(tri-n-butyltin)oxide	Haloperidol	Propylthiouracil
Bisphenol A	Halothane	Retinoids/vit.A/isotretinoin
Bromodeoxyuridine(5-)	Heptachlor	Salicylate
Butylated Hydroxy Anisol	Hexachlorobenzene	Tebuconazole
Butylated hydroxytoluene	Hexachlorophene	Tellurium (salts)
Cadmium	Hydroxyurea	Terbutaline
Caffeine	Imminodipropionitrile (IDPN)	Thalidomide
Carbamazepine	Ketamine	THC
Carbaryl	Lead	Toluene
Carbon monoxide	Lindane	Triamcinolone
Chlordecone	LSD	Tributyltin chloride
Chlordiazepoxide	Maneb	Trichlorfon
Chlorine dioxide	Medroxyprogesterone	Trichloroethylene
Chlorpromazine	Mepivacaine	Triethylenelead
Chlorpyrifos	Methadone	Triethyltin
Cocaine	Methanol	Trimethyltin
Colcemid	Methimazole	Trypan blue
Colchicine	Methylparathion	Urethane
Cypermethrin	Monosodium Glutamate	Valproate
Dexamethasone	MPTP	Vincristine
Diamorphine hydrochloride	Naloxone	

Sample Paragraph

DEXAMETHASONE
CAS Number: 50-02-2

Formula:



Dexamethasone is synthetic member of the glucocorticoid class of steroid hormones. It is used to treat inflammation and autoimmune conditions (e.g., rheumatoid arthritis), and to counteract side-effects of chemotherapy in cancer patients. Synthetic glucocorticoids, including dexamethasone, are also administered to women at risk for preterm labor to advance fetal maturation and reduce neonatal morbidity and mortality.

Numerous studies in animals have shown neurodevelopmental effects of perinatal dexamethasone treatment in rodents. Doses of 0.2 – 3 mg/kg (which encompasses the therapeutic range in humans) given to the pregnant dam during gestation or to the offspring postnatally alter neurogenesis and differentiation (Bohn, 1984; Carlos et al., 1992), decrease brain size and brain weight (DeKoskey et al., 1982; Carlos et al., 1992; Ferguson and Holson, 1999), and alter locomotor activity and learning and memory behavior (DeKoskey et al., 1982; Vicedomini et al., 1986; Ferguson et al., 2001; Kreider et al., 2005a). Relatively low doses (0.05 – 0.2 mg/kg) have also been shown to result in long-lasting changes in neurotransmitter systems and intracellular signaling (Kreider et al., 2005b; Kreider et al., 2006; Slotkin et al., 2006). Effects of dexamethasone, including decreased brain weight and hippocampal damage, have also been observed in nonhuman primates (reviewed in Coe and Lubach, 2005).

Human developmental neurotoxicity is associated with perinatal exposure to dexamethasone. Prenatal dexamethasone is routinely administered to mothers at risk for preterm delivery to reduce mortality and the incidence of respiratory distress syndrome and intraventricular hemorrhage in premature infants. Postnatal dexamethasone treatment in preterm infants is also used to reduce the risk and severity of chronic lung disease. A preponderance of epidemiologic and clinical evidence, however, indicates that both pre- and post-natal exposure to dexamethasone can result in an increased risk for cerebral palsy, decreased brain size, and long-term effects on cognition and behavior (reviewed in Baud, 2004; Purdy, 2004; Purdy and Wiley, 2004; Sloboda et al., 2005).

*Registration Eligibility Decision Documents (available online or via Freedom of Information Act)