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

W. Mundy[1], *S. Padilla*[1], *T. Shafer*[1], *M. Gilbert*[1], J. Breier[1,2], J. Cowden[1], *K. Crofton*[1], *D. Herr*[1], *K. Jensen*[1], *K. Raffaele*[3], N. Radio[4], and K. Schumacher[5].
[1]Neurotoxicology Div. U.S. EPA, RTP, NC 27711; [2]Curriculum in Toxicology, Univ. of N.C. at Chapel Hill, Chapel Hill, NC, 27514; [3] NCEA/ORD, U.S. EPA, Washington, DC, 20460; [4]Cellumen, Inc., Pittsburgh, PA. 15238; [5]U.S. EPA, Region 7, Kansas City, KS, 66101.

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:

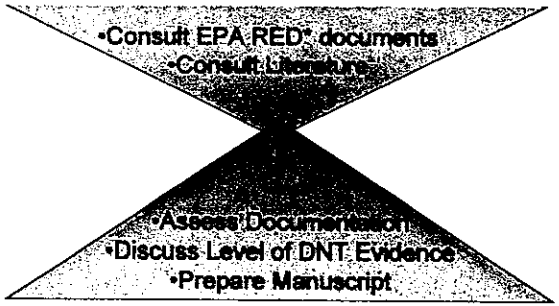
(1) no evidence: either there were no reports that met our criteria for evidence, or there were reports which showed no developmental neurotoxicity;
(2) minimal evidence: one report only or multiple reports from only one laboratory; or
(3) substantial evidence: reports from more than one laboratory.

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)



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.**

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

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:

- Head Circumference
- Brain Weight
- Exencephaly
- Brain Morphology
- Motor Activity
- Learning and Memory
- Grip Strength
- Negative Geotaxis
- Startle Response
- Righting Reflex
- Neurochemical Levels
- Receptor Affinity/Number

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

1,1,1-Trichloroethane
Abamectin
Acephate
Acetamiprid
ActinomycinD
Amicarbazone (MKH 3586)
Aminozole
Atorvastatin
Atrazine
Azinphos methyl
BAS 510 (Boscalid)
BAS 670H
Bifenthrin
Bismuth Ribromophenate
Brominated veg oil
Busulfan
Carbofuran
Carbon disulfide
Chlordane
Chlordimeform
Chlorfenapyr
Chlorite, sodium
CI-943 (Antipsychotic)
Clodinafop-propargyl
Clothianidin
Coumaphos
Cyfluthrin
Cyhalothrin
Cymoxanil
Denazol
DDT
Dexromoramide
Diaminotoluene (2,6-)
Dichloromethane (methylene chloride)
Dichlorvos (DDVP)
Dicrotophos
Difluoromethylornithine
Dimethoate
Dinoseb
Diphenhydramine
Disulfoton
Emamectin
Endosulphan
Endrin
EPTC (S-Ethyl dipropylthiocarbamate)
Ergotamine
Ethoxythanol (2-)
Ethylene dibromide
Ethylene oxide
Etofenprox
Fenamiphos
Fenitrothion
Fenvalerate
FK 33-824 (Synthetic enkephalin)
Flufenacet (thiaflumide)
Formaldehyde
Glufosinate ammonium
Glyphosate trimesium
Hexachoroplatinate (Na)
Imidacloprid
Ivermectin
Lasofoxifene
Levo-alpha-acetylmethadol
Lidocaine
Malathion
Mancozeb
Maytansine
Methamidaphos
Methyl Ethyl Ketone
MNDA
Molinate
Naled
n-Hexane
Nickel carbonyl
Perchlorate
Phorate (BAS 226 I)
Picrotoxin
Primidone
Profenofos
Prothioconazole
Selenium compounds
Simvastatin
Spirodiclofen
Succamir
Terbufos
tert-Butylhydroquinone, 2-
Tetrachloethylene
Tetracycline
Thiamethoxam
Tributos (DEF)
Triethylene glycol dimethyl ether
Trimethadione
Triphenyl phosphate
VM-26 (Teniposide)
VP-16-213 (Etoposide)

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

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

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 (DeKosky et al., 1982; Carlos et al., 1992; Ferguson and Holson, 1999), and alter locomotor activity and learning and memory behavior (DeKosky et al., 1982; Vicedomini et al., 1985; 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 hemorrage 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).