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Synopsis of published literatures on health effects of Endosulfan

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1) NERVOUS SYSTEM

1.1	**Title:** **Developmental exposure to pesticides zineb and/or endosulfan renders the nigrostriatal dopamine system more susceptible to these environmental chemicals later in life** **Authors and their affiliations:** Zhenquan Jia a, Hara P. Misra a,b,* a Department of Biomedical Sciences and Pathobiology, College of Veterinary Medicine, Virginia Polytechnic Institute and State University, Blacksburg, VA 24061, USA b Edward Via Virginia College of Osteopathic Medicine, Virginia Tech Corporate Research Center, 2265 Kraft Drive, Blacksburg, VA 24060, USA **Published in:** **NeuroToxicology 28 (2007) 727–735**	**Major Findings:** The study was to test the hypothesis that exposure to pesticides such as endosulfan and/or zineb during critical periods of postnatal development could result in neuronal dysfunction and enhance the impact of these pesticides during exposure as adults. The findings support our hypothesis that **exposure** to pesticides such as endosulfan and zineb during critical periods of postnatal development contributes to neurotransmitter changes upon re-challenge in adulthood.

1.2	**Title:** **Endosulfan Poisoning and Chronic Brain Syndrome** **Authors and their affiliations:** Dov R. Aleksandrowicz Shalvata Psychiatric Center Hod Hasharon, Israel **Published in:** **Arch. Toxicol. 43, 65-68 (1979)**	**Major Findings:** This report describes a case of chronic brain syndrome following poisoning by **endosulfan**; **it is believed to be the first recorded case of such a complication due to that compound.**
1.3	**Title:** **Effects of in utero and lactational exposure to endosulfan in prefrontal cortex of male rats** **Authors and their affiliations:** Teresa Cabaleiro, Ana Caride, Alejandro Romero, Anunciaci´on Lafuente ∗ Laboratorio de Toxicolog´ıa, Facultad de Ciencias, Universidad de Vigo, Campus de Orense, Las Lagunas, 32004 Orense, Spain **Published in:** **Toxicology Letters 176 (2008) 58–67**	**Major Findings:** The possible **neurotoxic effects of** the organochlorine pesticide **endosulfan** have been **evaluated on male offspring rats exposed in utero and during lactation.** The developing nervous system is proposed to be a potentially sensitive target for pesticide exposure (Tilson, 1998, 2000; Nakai and Satoh, 2002; Shafer and Meyer, 2005) Summarizing, **in utero and lactational treatment to endosulfan induces several alterations in content and metabolism of amino acids and biogenic amines in prefrontal cortex** in male rats during the development.

		These variations are age- and dose-dependent and **they could be related to several alterations in the important functions in which the prefrontal cortex is involved such as cognitive tasks, selective attention, short term working memory, response inhibition, behavioural flexibility, etc.**
1.4	**Title:** **Effects of endosulfan on brain acetyl-cholinesterase activity in juvenile bluegill sunfish** **Authors and Affiliations:** Hiran M. Dutta_ and Dane A. Arends Department of Biological Sciences, Kent State University, Kent, OH 44242, USA **Published in:** Environmental Research 91 (2003) 157–162	**Major Points:** The effects of endosulfan upon brain acetylcholinesterase (AChE) activity were measured in juvenile bluegill sunfish (Lepomis macrochirus). **The duration of exposure was related to the reduction in the AChE activities which reflected the biotoxicity of endosulfan.** The changes in the AChE activities will certainly affect the normal behavior of the juvenile bluegill which is **detrimental to their very existence in the natural habitat.**
1.5	**Title:** **Selective involvement of basal ganglia and occipital cortex in a patient with acute endosulfan poisoning** **Authors and Affiliations:** Department of Neurology, Sunjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India	**Major Points:** We report a teenage girl with acute endosulfan poisoning who developed psychosis, generalized tonic-clonic seizures, myoclonic jerks, cortical blindness and limb rigidity. Serial magnetic resonance imaging (MRI) **showed bilateral reversible lesions localized to caudate nucleus, putamen and occipital cortex;** internal capsule and thalamus were spared.

	Department of Radiology, Sunjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India Department of Neuroophthalmology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India **Published in:** **Journal of Neurological Sciences 147 (1997) 209-213**	This selective involvement may have a bearing on mechanisms underlying endosulfan toxicity.
1.6	**Title:** **Association of selected persistent organic pollutants in the placenta with the risk of neural tube defects** **Authors and their affiliations** Ren, A. Qiu, X. Jin, L. Ma, J. Li, Z. Zhang, L. Zhu, H. Finnell, R. H. Zhu, T. Institute of Reproductive and Child Health and Ministry of Health Key Laboratory of Reproductive Health, Peking University Health Science Center, Beijing 100191, China. **Published in:** Proc Natl Acad Sci U S A. 2011 Jul 18	**Major Findings:** The case-control study was performed to explore the association between placental levels of selected POPs and risks for neural tube defects (NTDs) in a Chinese population with a high prevalence of NTDs. Placental concentrations were analyzed by gas chromatography-mass spectrometry. The medians of polycyclic aromatic hydrocarbons (PAHs), o,p'-isomers of dichlorodiphenyltrichloroethane (DDT) and metabolites, alpha- and gamma-hexachlorocyclohexane (HCH), and **alpha-endosulfan** were significantly higher in case placentas than in controls. Concentrations above the median were associated with a 4.52-fold [95% confidence interval (CI), 2.10-9.74) increased risk for any NTDs, and 5.84- (95% CI, 2.28-14.96) and 3.71-fold (95% CI, 1.57-8.79) increased risks for anencephaly and spina bifida, respectively. A **dose-response relationship** was observed for anencephaly and spina bifida subtypes.

1.7	**Title:** **The environmental pollutant endosulfan disrupts cerebral cortical function at low doses** **Authors and their affiliations** Scremin, Oscar U Chialvo, Dante R Lavarello, Simona Berra, Hector H Lucero, Miguel A Netherlands Instituto de Toxicologia Agraria de Rosario, Facultad de Ciencias Medicas, UNR, Santa Fe 3100, Rosario CP2000, Argentina. oscremin@ucla.edu **Published in:** Neurotoxicology. 2011 Jan;32(1):31-7. Epub 2010 Dec 7.	Endosulfan can induce convulsions that could lead to brain damage. The variability and lack of specificity of neurological signs and symptoms in the pre-convulsive stages makes early diagnosis difficult. We sought to determine if electrophysiological exploration of the cerebral cortex could yield objective signs of endosulfan intoxication at levels that do not elicit convulsions. EEG power and the evoked potentials (EP) to electrical stimulation were studied over the contralateral (S1CL) and homolateral (S1HL) cortical somatosensory areas and the contralateral visual area (V1CL). Endosulfan induced a dose-related increase in EPs at all sites. In conclusion**, endosulfan induced a large increase of cortical evoked potentials amplitudes at doses that did not elicit convulsions.** These responses **could be used as a non-invasive diagnostic tool to detect low-level endosulfan intoxication in humans and to help establish the NOAEL and LOAEL levels of this pollutant.**

2) REPRODUCTIVE SYSTEM		
2.1	**Title:** **A method to determine residue levels of persistent organochlorine pesticides in human milk from Indonesian women** **Authors and their affiliations:** Emma R. Burke a, Alexis J. Holden a,*, Ian C. Shaw b a Department of Environmental Management, University of Central Lancashire, Preston PR1 2HE, UK b Environmental Science &Research Institute, 27 Creyke Rd, Christchurch, New Zealand **Published in:** **Chemosphere 50 (2003) 529–535** 2002 Elsevier Science Ltd	**Major Findings:** A method has been developed for the analysis of organochlorine pesticides in human milk using solvent extraction, Florisil_ solid phase extraction clean-up and analysis by gas chromatography with an electron capture detector. **There was no significant difference (at the 95% confidence level) in levels of pesticides between urban and rural areas**
2.2	**Title:** **Endosulfan sulphate interferes with reproduction, embryonic development and sex differentiation in Daphnia magna** **Authors and their affiliations:** P. Palma a,c,_, V.L. Palmaa, R.M. Fernandes a, A.M.V.M. Soares b, I.R. Barbosa a Departamento de Cieˆncias do Ambiente, Escola Superior	**Major Findings:** The aim of this study was to evaluate the possible effects promoted by endosulfan sulphate in changes on the life cycle, embryo development and sex differentiation of Daphnia magna. **Endosulfan sulphate promoted a significant decrease of the offspring number in all concentrations.** Results showed a reduction of the size of females, together with a decrease in moulting frequency. Furthermore, **an increase in embryo deformities was observed at all**

	Agra´ria de Beja, Beja 7800-295, Portugal b CESAM & Departamento de Biologia da Universidade de Aveiro, Aveiro 3810-193, Portugal c Centro de Estudos Farmaceˆuticos, Faculdade de Farma´cia, Universidade de Coimbra, Rua do Norte, Coimbra 3000-295, Portugal **Published in:** **Ecotoxicology and Environmental Safety 72 (2009) 344– 350**	**concentrations tested.** Above a concentration of 91.7 mgL_1 there was an increased production of males. The results suggest that **endosulfan sulphate interferes with the life cycle and sex determination** of the crustacean D. magna.
2.3	**Title:** **Persistent Pesticides in Human Breast Milk and Cryptorchidism** **Authors and their affiliations:** Ida N. Damgaard,1 Niels E. Skakkebæk,1 Jorma Toppari,2 Helena E. Virtanen,2 Heqing Shen,3 Karl-Werner Schramm,3 Jørgen H. Petersen,1,4 Tina K. Jensen,1 Katharina M. Main 1University Department of Growth and Reproduction, Copenhagen, Denmark; 2Departments of Physiology and Pediatrics, University of Turku, Turku, Finland; 3GSF-National Research Center for Environmental and Health, Institute for Ecological	**Major Findings:** **Eight organochlorine pesticides** (including Endosulfan) were **measured** in all samples (medians; nanograms per gram lipid) for cases/controls. Statistical analysis showed that pesticide levels in breast milk were significantly higher in boys with cryptorchidism ($p = 0.032$). In conclusion, our study suggests **an association between congenital cryptorchidism and persistent organochlorine pesticides present in mothers' breast milk**. **Prenatal exposure to persistent organochlorine pesticides may adversely affect testicular descent in boys.**

	Chemistry, euherberg, Germany; 4Department of Biostatistics, University of Copenhagen, Denmark **Published in:** **Environ Health Perspect 114:1133–1138 (2006).**	
2.4	**Title:** **Organochlorine pesticide residue** **levels and oxidative stress in preterm delivery cases** **Authors and their affiliations:** Rahul Pathak1, Sanvidhan G Suke1, Tanzeel Ahmed1, Rafat S Ahmed1, AK Tripathi1, Kiran Guleria2, CS Sharma3, SD Makhijani3 and BD Banerjee1 1 Environmental Biochemistry and Immunology laboratory, Department of Biochemistry, University College of Medical Sciences & G.T.B. Hospital (University of Delhi), Delhi, India 2 Department of Obstetrics and Gynecology, University College of Medical Sciences & G.T.B. Hospital (University of Delhi), Delhi, India 3 Instrumentation and Bio-Labs, Central Pollution Control Board, Ministry of Environment and Forest, Delhi, India	**Major Findings:** The aim of the present study was to analyze the OCP residues in maternal and cord blood of women and assess the levels of different non-enzymatic oxidative stress markers as well as to establish correlation with OCP levels, if any. Levels of OCPs like Hexachlorocyclohexane (HCH), **endosulfan,** and DDT were analyzed by gas chromatography. Non-enzymatic oxidative stress was measured. In conclusion, our results suggest that higher levels of some of the OCP (like **Endosulfan**) **may be associated with Preterm Delivery and increased oxidative stress.**

	Published in: **Human and Experimental Toxicology 29(5) 351–358**	
2.5	**Title:** **Endosulfan and its metabolites in fertile women, placenta, cord blood, and human milk** **Authors and their affiliations:** Isabel Cerrilloa, Alicia Granadaa, Marı´a-Jose´ Lo´ pez-Espinosaa, Begon˜ a Olmosa, Margarita Jime´neza, Africa Can˜ ob, Nicolas Oleaa,_, Marı´a Fa´ tima Olea-Serranoc aLaboratory of Medical Investigations, Department of Radiology, School of Medicine, Hospital Clinico, University of Granada, 18071 Granada, Spain bGynecology & Obstetric Service, Hospital Cli´nico, Granada, Spain cFood Sciences Department, University of Granada, Granada, Spain **Published in:** **Environmental Research 98 (2005) 233–239**	**Major Findings:** The present study **investigated the presence of endosulfan I, endosulfan II, and endosulfan metabolites in fatty and non-fatty tissues** and fluids from women of reproductive age and children in Southern Spain. The highest concentration of commercial endosulfan I and endosulfan II was found in adipose tissue, with a mean value (I+II) of 17.72 ng/g lipid, followed by human milk, with a mean value (I+II) of 11.38 ng/mL milk. This study suggests that **exposure from mother to child is a common event, both in utero and via breastfeeding,** due to the high frequency of exposure of women of reproductive age.
2.6	**Title:** **Effect of Endosulfan on Male Reproductive Development** **Authors and Affiliations:** Habibullah Saiyed,1 Aruna	**Major Points:** A study to examine the relationship between environmental endosulfan exposure and reproductive development in male children and adolescents. The study population was composed of 117

	Dewan,1 Vijay Bhatnagar,1 Udyavar Shenoy,2 Rathika Shenoy,2 Hirehall Rajmohan,3 Kumud Patel,1 Rekha Kashyap,1 Pradip Kulkarni,1 Bagalur Rajan,3 and Bhadabhai Lakkad1 1National Institute of Occupational Health (Indian Council of Medical Research), Meghani Nagar, Ahmedabad, India; 2Department of Pediatrics, Kasturba Medical College, Mangalore, India; 3Regional Occupational Health Research Centre, Bangalore, India **Published in:** **VOLUME 111 | NUMBER 16 | December 2003 • Environmental Health Perspectives**	male schoolchildren (10–19 years of age) of a village situated at the foothills of cashew plantations. The study parameters included recording of clinical history, physical examination, sexual maturity rating (SMR) according to Tanner stages, and estimation of serum levels of testosterone, luteinizing hormone (LH), follicle-stimulating hormone, and endosulfan residues. Our study **results suggest that endosulfan exposure in male children may delay sexual maturity and interfere with sex hormone synthesis.**
2.7	**Title:** **Peripheral precocious puberty in a 4-month-old girl: role of pesticides?** **Authors and their affiliations** Gaspari, L. Paris, F. O. Jeandel, C. Sultan, C. Unit d'Endocrinologie-Gyncologie Pediatrique, Service de Pediatrie 1, Hospital Arnaud-de-Villeneuve, CHU Montpellier, University Montpellier I,	**Major Findings:** A 4-month-old girl presented with sexual development, including breast enlargement, menstruation, uterine length of 69?mm at ultrasonography, and dramatically high estrogen bioactivity, but no growth acceleration, pubic hair, pelvis masses or adrenal tumors. Gas chromatography with an electron capture detector and mass spectrometry detected pesticides (DDT, lindane and **endosulfan sulpfate**) in plasma from the infant, the mother, and the 38-year-old father, who reported a dramatic decrease in libido, and in soil samples from their farm.

	Montpellier, France. **Published in:** Gynecol Endocrinol. 2011 Feb 9.	The precocious sexual development was probably caused by the estrogen activity of the environmental contamination by tons of pesticides stored in the family farm.

3) ENDOCRINE SYSTEM		
3.1	**Title:** **Effect of pesticides on estrogen receptor transactivation in vitro: A comparison of stable transfected MVLN and transient transfected MCF-7 cells** **Authors and their affiliations:** Eva C. Bonefeld-Jorgensen ∗, Heidi T. Gr¨unfeld, Irene M. Gjermandsen Unit of Environmental Biotechnology, Department of Environmental and Occupational Medicine, University of Aarhus, Vennelyst Boulevard 6, DK-8000 Aarhus, Denmark **Published in:** **Molecular and Cellular Endocrinology 244 (2005) 20–30**	**Major Findings:** The **estrogenic potential of four pesticides** (endosulfan, prochloraz, tolchlofos-methyl and propamocarb) was **compared** in parallel with 17_-estradiol (E2) by reporter constructs in transient transfected MCF-7BUS and in stable transfected MVLN cells. **In MVLN cells, endosulfan, prochloraz, tolchlofos-methyl and propamocarb caused cytotoxic responses at concentrations higher than 10, 25, 25 and 100 _M, respectively.**
3.2	**Title:** **Xenoestrogen-Induced ERK-1 and ERK-2 Activation via Multiple Membrane-Initiated Signaling Pathways** **Authors and their affiliations:**	**Major Findings:** The objective of the study was to investigate the ability of some of the estrogen mimetics (belonging to major classes of environmental estrogens) to produce rapid activation of ERKs via various signaling pathways in the

	Bulayeva, Nataliya N;Watson, Cheryl S Department of Human Biological Chemistry and genetics, University of Texas Medical Branch, Galveston, Texas, USA **Published in:** **Environmental Health Perspectives; Nov 2004; 112, 15; ProQuest pg. 1481**	GH3/B6/F10 prolactinoma cell lines. **Endosulfan was able to produce phosphorylation at almost all tested concentrations.** Basically two patterns of stimulations were seen: Compounds active **in both subpicomolar and nanomolar ranges** (Endosulfan, nonylphenol and coumestrol) versus compounds active only in the nanomolecular range (DDE and dieldrin).
3.3	**Title:** **Effects of Currently Used Pesticides in Assays for Estrogenicity, Androgenicity, and Aromatase Activity in Vitro** **Authors and their affiliations:** Helle Raun Andersen,* Anne Marie Vinggaard,† Thomas Høj Rasmussen,* Irene Marianne Gjermandsen,‡ and Eva Cecilie Bonefeld-Jørgensen‡ *Environmental Medicine, Institute of Public Health, University of Southern Denmark, Odense, Winsløwparken 17, DK-5000 Odense C, Denmark; †Institute of Food Safety and Toxicology, Division of Biochemical and Molecular Toxicology, Danish Veterinary and Food Administration, Mørkhøj Bygade 19, DK-2860 Søborg, Denmark; and ‡Department of Environmental and Occupational Medicine, Unit of Environmental Biotechnology,	**Major Findings:** **Twenty-four pesticides were tested for interactions with the estrogen receptor (ER) and the androgen receptor (AR) in transactivation assays.** **The two organochlor insecticides dieldrin and Endosulfan increased cell proliferation and ER transactivation gene response** in MCF-7 cells significantly at 5 and 1 _M, respectively. Both compounds induced maximum response at 25 _M, whereas higher concentrations resulted in a decreased response due to cytotoxicity. **In both assays, the response induced by endosulfan was higher than the response induced by dieldrin.** Endosulfan potentiated the 17_-estradiolinduced proliferation when it was tested together with a concentration of 17_-estradiol causing a submaximum response. Dieldrin did not enhance the 17_-estradiol-induced response in any of the assays.

	University of Aarhus, Building 260, Vennelyst Boulevard 6, DK-8000 Aarhus C, Denmark **Published in:** **Toxicology and Applied Pharmacology 179, 1–12 (2002)**	
3.4	**Title:** **Endosulfan effects on pituitary hormone and both nitrosative and oxidative stress in pubertal male rats** **Authors and Affiliations:** A. Caride, A. Lafuente∗, T. Cabaleiro Laboratorio de Toxicología, Facultad de Ciencias, Universidad de Vigo, Campus de Orense, Las Lagunas, 32004 Orense, Spain **Published in:** **Toxicology Letters 197 (2010) 106–112**	**Major Points:** The study was undertaken to investigate in pubertal male rats possible **effects of endosulfan** administered throughout lactation and gestation **on: (a) pituitary gene expression of prolactin, luteinizing hormone (LH), growth hormone (GH) and thyroid stimulating hormone (TSH); and (**b) circulating levels of these hormones. In pubertal male rat, prenatal and **lactational exposure to endosulfan modifies expression and release of prolactin, LH, GH and TSH**, and pituitary NOS1 and NOS2 mRNA levels, suggesting that **nitrosative stress can be implicated in the endocrine toxicity of endosulfan at pituitary level.**

3.5	**Title:** **Screening of some anti-progestin endocrine disruptors using a recombinant yeast based in vitro bioassay** **Authors and Affiliations:** Shamba Chatterjee a,1, Vikas Kumar a,1, Chandrajeet B. Majumder b, Partha Roy a,* a Molecular Endocrinology Laboratory, Department of Biotechnology, Indian Institute of Technology Roorkee, Roorkee 247 667, Uttarakhand, India b Fluid Particle Research Laboratory, Department of Chemical Engineering, Indian Institute of Technology Roorkee, Roorkee 247 667, Uttarakhand, India **Published in:** **Toxicology in Vitro 22 (2008) 788–798**	**Major Points:** **About 7 different chemicals** (mostly pesticides or their metabolites) **like** DDT and its metabolites, nonylphenol, **endosulfan** were screened in this assay system for their role in transactivation **and they were all found to be anti-progestative**.
3.6	**Title:** Circulating thyroid hormone levels and iodothyronine deiodinase activities in Nile tilapia (Oreochromis niloticus) following dietary exposure to Endosulfan and Aroclor **Authors and Affiliations:** Ana Maria Coimbraa,b,*, Maria Armanda Reis-Henriquesa,b, Veerle M. Darrasc a) ICBAS-Instituto de Cieˆncias Biome´dicas de Abel Salazar,	**Major Points:** We evaluated the effects of two organochlorinated environmental contaminants, Endosulfan and Aroclor 1254 on peripheral thyroid hormone metabolism and thyroid hormone plasma levels in Nile tilapia (Oreochromis niloticus). It is concluded that dietary exposure of tilapia to **Endosulfan** or Aroclor 1254 **can lead to changes in circulating thyroid hormone levels and/or in peripheral thyroid hormone**

	Laborato´rio de Fisiologia Aplicada, Largo do Prof. Abel Salazar 2, 4099-003, Porto, Portugal b) CIIMAR-Centro Interdisciplinar de Investigac¸a˜o Marinha e Ambiental, Laborato´ rio de Toxicologia Ambiental, Rua dos Bragas 289, 4050-123, Porto, Portugal c) Laboratory of Comparative Endocrinology, Zoological Institute K.U. Leuven, Naamsestraat 61, B-3000 Leuven, Belgium **Published in:** **Comparative Biochemistry and Physiology, Part C 141 (2005) 8 – 14**	**metabolism.** The changes in hormone metabolism differ between tissues, eventually reflecting tissue-specific differences in adaptation.
3.7	**Title:** **Human Exposure to Endocrine-Disrupting Chemicals and Prenatal Risk Factors for Cryptorchidism and Hypospadias: A Nested Case–Control Study** **Authors and Affiliations:** Mariana F. Fernandez,1 Begoña Olmos,1 Alicia Granada,1 Maria José López-Espinosa,1 José-Manuel Molina-Molina,1 Juan Manuel Fernandez,2 Milagros Cruz,3 Fátima Olea-Serrano,4 and Nicolás Olea1 1Laboratory of Medical Investigations, 2Department of Pediatrics, and 3Department of Gynecology and Obstetrics, San Cecilio UniversityHospital, Granada, Spain; 4Department of Nutrition, University of Granada, Granada,	**Major Points:** In this study we aimed to determine whether the combined effect of environmental estrogens measured as total effective xenoestrogen burden (TEXB) is a risk factor for male urogenital malformations**.** **We found an increased risk for male urogenital malformations related to the combined effect of environmental estrogens in placenta.**

	Spain **Published in:** **VOLUME 115	SUPPLEMENT 1	December 2007 • Environmental Health Perspectives**	
3.8	**Title:** **Endocrine disrupters and human puberty** **Authors and Affiliations:** E. Den Hond and G. Schoeters Department of Toxicology, VITO (Flemish Institute for Technological Research), Mol, Belgium **Published in:** **international journal of andrology 29 (2006) 264–271**	**Major Points:** Epidemiological research studying the effect of endocrine disrupters on the onset of puberty is summarized. **In girls, earlier age at menarche** was reported after exposure to polychlorinated biphenyls (PCBs), poly brominated biphenyls (PBBs), persistent pesticides (DDT, endosulfan) and phthalate esters. **In boys**, exposure to PCBs, PCDFs or the pesticide **endosulfan** was associated with **delayed puberty or decreased penile length.**
3.9	**Title:** **Oxidative stress and loss of cortisol secretion in adrenocortical cells of rainbow trout (Oncorhynchus) exposed in vitro to endosulfan, an organochlorine pesticide** **Authors and Affiliations:** J. Dorval, V.S. Leblond, A. Hontela * De´partement des Sciences Biologiques, Universite´ du Que´bec a` Montre´al, TOXEN Research Centre, C.P. 8888, succ. Centre-ville, Montre´al, Que´., Canada H3C 3P8 **Published in:** **Aquatic Toxicology 63 (2003)**	**Major Points:** The effects of endosulfan on cortisol secretion, cell viability, antioxidants and lipid peroxidation were investigated. The in vitro **study identified endosulfan as a chemical inducing a loss of secretory responses in teleost adrenocortical steroidogenic cells and alterations in the activity of enzymes known to be involved in oxidative stress pathways.** **Moreover**, the significant increase in lipid hydroperoxides levels provided **further evidence for endosulfan-induced oxidative stress.**

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3.10	**Title:** **Effect of in vitro estrogenic pesticides on human oestrogen receptor _ and _ mRNA levels** **Authors and Affiliations:** H.T. Grünfeld, E.C. Bonefeld- Jorgensen∗ *Unit of Environmental Biotechnology, Department of Environmental and Occupational Medicine, University of Aarhus,* *Vennelyst Boulevard 6, DK-8000 Aarhus, Denmark* **Published in:** **Toxicology Letters 151 (2004) 467–480**	**Major Points:** Nine widely distributed pesticides were recently demonstrated to possess potential estrogenic properties in oestrogen receptor (ER) transactivation and/or E-screen assays. This **study demonstrated** that **organochlor** and organo-phosphorous pesticides possess the **ability to interfere with the ER_ and ER_ mRNA steady state levels.**
3.11	**Title:** **Differential estrogenic effects of the persistent organochlorine pesticides dieldrin, endosulfan, and lindane in primary neuronal**	**Major Findings:** The organochlorine chemicals **endosulfan**, dieldrin, and gamma-hexachlorocyclohexane (lindane) are persistent pesticides to which people are **exposed mainly via diet**. Their

	cultures **Authors and their affiliations** Briz, Victor Molina-Molina, Jose-Manuel Sanchez-Redondo, Sara Fernandez, Mariana F Grimalt, Joan O Olea, Nicolas Rodriguez-Farre, Eduard Sunol, Cristina Department of Neurochemistry and Neuropharmacology, Institut d'Investigacions Biomediques de Barcelona, Consejo Superior de Investigaciones Cientificas, Institut d'investigacions Biomediques August Pi i Sunyer, E-08036 Barcelona, Spain. **Published in:** Toxicol Sci. 2011 Apr;120(2):413-27. Epub 2011 Jan 27.	antagonism of the gamma-aminobutyric acid-A (GABA(A)) receptor makes them convulsants. They are also **endocrine disruptors** because of their interaction with the estrogen receptor (ER). Here, we study the effects of dieldrin, endosulfan, and lindane on ERs in primary cultures of cortical neurons (CN) and cerebellar granule cells (CGC). All the compounds tested inhibited the binding of [(3)H]-estradiol to the ER in both CN and CGC, with dieldrin in CGC showing the highest affinity. Moreover, extracts of CN treated with endosulfan, dieldrin, or lindane **induced cell proliferation in MCF-7 human breast cancer-derived cells**. Overall, the observed alterations on ER-mediated signaling and ER levels in neurons might contribute to the neurotoxicity of these organochlorine pesticides.
3.12	**Title:** **Prenatal exposure to organochlorine pesticides and TSH status in newborns from Southern Spain** **Authors and their affiliations** Freire, Carmen ,Lopez-Espinosa, Maria-Jose,Fernandez, Marieta Molina-Molina, Jose-Manuel Prada, Remedios, Olea, Nicolas	**Major Findings:** OBJECTIVE: To investigate the association between prenatal exposure to organochlorine pesticides (OCPs) and thyroid-stimulating hormone (TSH) levels in male newborns. METHODS: Exposure to 17 OCPs was analyzed in 220 placentas from a male birth cohort in Southern Spain, and TSH was measured in the umbilical cord blood. OCP concentrations were quantified by gas chromatography and mass

	Netherlands Laboratory of Medical Investigations, San Cecilio University Hospital, University of Granada, CIBER de Epidemiologia y Salud Publica (CIBERESP), Av. Madrid s/n, 18071 Granada, Spain. **Published in:** Sci Total Environ. 2011 Aug 15;409(18):3281-7.	spectrometry. Multivariate regression analysis was conducted to examine the association between pesticide exposure and neonatal TSH levels, adjusting for confounders. RESULTS: Newborn boys with higher exposure to endrin in placenta had higher odds of TSH cord blood levels ,higher prenatal exposure to **endosulfan-sulfate** was associated with lower odds of TSH >/=5mU/L. A marginally significant negative association was found between TSH and hexachlorobenzene levels. No association was found between TSH and the remaining pesticides. CONCLUSIONS: **Early exposure to certain environmental chemicals with endocrine-disruption activity may interfere with neonatal thyroid hormone status;** however, the pattern of interference is not yet clearly elucidated.
3.13	**Title:** Estrogen-like endocrine disrupting chemicals affecting puberty in humans--a review **Authors and Affiliations:** Roy, Jonathan R , Chakraborty, Sanjoy Chakraborty, Tandra R Department of Biology, Adelphi University, Garden City, New York, NY 11530, USA. **Published in:** Med Sci Monit. 2009	**Major Points:** Estrogen-like endocrine disrupting chemicals (EEDC) are exogenous, man-made chemicals that alter the functions of the endocrine system and cause various health defects by interfering with the synthesis, metabolism, binding or cellular responses of natural estrogens. Major EEDCs found abundantly in our environment include; Endosulfan, DDT, dioxin, polychlorinated biphenyls (PCBs), bisphenol A (BPA), polybrominated biphenyls (PBB), phthalate esters, atrazine and zeranol**. In girls, EEDCs**

	Jun;15(6):RA137-45.	**has been linked to earlier menarche, abnormal breast development in pre-pubertal, earlier menarche, thelarche and earlier pubic hair stage. In males, endosulfan affects pubertal boys by slowing down the timing of reproductive maturation.** This article provides a possible structure-function relation of the above mentioned EEDCs which interfere with sexual development during puberty.
3.14	**Title:** **Endosulfan effects on pituitary hormone and both nitrosative and oxidative stress in pubertal male rats** **Authors and Affiliations:** Caride, A, Lafuente, A, Cabaleiro, T Laboratorio de Toxicologia, Facultad de Ciencias, Universidad de Vigo, Campus de Orense, Las Lagunas, 32004 Orense, Spain **Published in:** Toxicol Lett. 2010 Aug 16;197(2):106-12. Epub 2010 May 13.	**Major Points:** The present study was undertaken to investigate the possible effects of endosulfan on: (a) pituitary gene expression of prolactin, luteinizing hormone (LH), growth hormone (GH) and thyroid stimulating hormone (TSH); (b) circulating levels of these hormones; and (c) expression of nitric oxide synthase 1 and 2 (NOS1 and NOS2), and heme oxygenase-1 (HO-1) at pituitary level. We can conclude that in pubertal male rat, prenatal and lactational exposure to **endosulfan modifies expression and release of prolactin, LH, GH and TSH, and pituitary NOS1 and NOS2 mRNA levels, suggesting that nitrosative stress can be implicated in the endocrine toxicity of endosulfan at pituitary level.**

4) IMMUNE SYSTEM

4.1	**Title:** **Determination of the immunotoxic potential of pesticides on functional activity of sheep leukocytes in vitro** **Authors and Affiliations:** Juraj Pistl *, Nata´lia Kovalkovicˇova´, Vanda Holovska´, Jaroslav Lega´th, Ivan Mikula Department of Microbiology and Immunology, University of Veterinary Medicine, 041 81 Kosˇice, Slovakia **Published in:** Toxicology 188 (2003) 73_/81	**Major Points:** The effect of eight pesticides with different chemical structure (atrazine, bentazone, chloride-zone, dichlofluanid, **endosulfan**, MCPA, simazine, triallate) on sheep peripheral blood phagocytes and lymphocytes was examined. Three of the pesticides tested **suppressed both, the metabolic activity of phagocytes and mitogenic activation of lymphocytes** (dichlofluanid, endosulfan and simazine).
4.2	**Title:** **Toxic effects of endosulfan on blood lymphocyte subsets in adult rats** **Authors and Affiliations:** A. Lafuente, T. Cabaleiro, A. Caride, A. Romero *Laboratorio de Toxicolog´ıa, Facultad de Ciencias, Universidad de Vigo, Campus de Orense, Las Lagunas s/n, 32004-Orense, Spain* **Published in:** **Toxicology Letters 164S (2006) S1–S324**	**Major Points:** The objective was to evaluate possible immune alterations induced by endosulfan exposure during pregnancy and lactation in both male and female adult rats. The results suggest that **endosulfan exposure** during pregnancy and lactation could **modify humoral immunity** in offspring adulthood, and that **females** are **more susceptible** to this pesticide because their cellular immunity was also altered.

5) GENOTOXICITY, CYTOTOXICITY AND TERATOGENICITY

5.1	**Title :** **Comet assay in phytoplankton as biomarker of genotoxic effects of environmental pollution** **Authors and their affiliations:** Akcha a,*, G. Arzul a, S. Rousseau a, M. Bardouil b aIFREMER, Laboratoire d'Ecotoxicologie, Rue de l'Ile d'Yeu, 44311 Nantes Cedex 03, France b IFREMER, Laboratoire Phycotoxines, Rue de l'Ile d'Yeu, 44311 Nantes Cedex 03, France **Published in:** **Marine Environmental Research 66 (2008) pg: 59–61** journal homepage: www.elsevier.com/locate/marenvrev _ 2008 Elsevier Ltd.	**Major Findings:** **Genotoxicity was observed from 1 lg/L of endosulfan and was not concentration dependent.** **Endosulfan exposure resulted in DNA strand breaks from the concentration of 1 lg/L ($p < 0.05$), but effect did not appear to be concentration dependent**
5.2	**Title :** **Endosulfan Decreases Cell Growth and Apoptosis in Human HaCaT Keratinocytes:Partial ROS-Dependent ERK1/2 Mechanism** **Authors and their affiliations:** SEBASTIEN ANTHERIEU,1* NATHALIE LEDIRAC,1 ANNE-PASCALE LUZY,2 PHILIPPE LENORMAND,3 JEAN-CLAUDE CARON,2 AND ROGER RAHMANI1* 1 INRA, UMR 1112 ''Re´ponses des Organismes aux Stress Environnementaux'', Equipe de Toxicologie Cellulaire, Mole´culaire et Ge´nomique, Sophia-Antipolis, France 2 Galderma R&D, Les Templiers, Biot, France 3 Institute of Signaling, Developmental Biology and Cancer Research, CNRS-UMR 6543, Centre Antoine Lacassagne, Nice,	**Major Findings:** This study was designed to assess the mitogenic, apoptogenic, and genotoxic effects of endosulfan on the HaCaT cell line. **Endosulfan** has been shown to generate transient reactive oxygen species (ROS), and blocking this oxidative stress by N-acetyl cysteine (NAC) strongly prevented both persistent nuclear ERK1/2 phosphorylation and cell growth decrease. Additional experiments demonstrated that unchanged endosulfan rather than its metabolites has **mutagenic** effects and **increased DNA strand breaks** in human

	France **Published in:** **J. Cell. Physiol. 213: 177–186, 2007.**	keratinocytes. In conclusion, the results show that human keratinocytes are **more affected by a chronic** than an acute **exposure** to endosulfan. On the whole, our findings demonstrate that endosulfan **disrupts epidermal homeostasis by two concomitant independent mechanisms:** a ROS-dependent mechanism responsible for DNA damage and decrease in cell proliferation, and a ROS-independent inhibition of apoptosis that could contribute to mutant cell survival and therefore have possible carcinogenic effects.
5.3	**Title :** **Analysis of Endosulfan and Its Metabolites in Human Serum Using Gas Chromatography–Tandem Mass Spectrometry** **Authors and their affiliations:** F.J. Arrebola1, J.L. Martínez Vidal1,*, and A. Fernández-Gutiérrez2 1 Department of Analytical Chemistry, University of Almería, 04071 Almería, Spain 2 Department of Analytical Chemistry, University ofGranada, 18071 Granada, Spain **Published in:** **Journal of Chromatographic Science, Vol. 39, May 2001**	**Major Findings:** A new analytical method combining solid-phase extraction and gas chromatography–tandem mass spectrometry used to determine the insecticide endosulfan as well as its metabolites endosulfan-ether, -lactone, and -sulfate in human serum. The **mean levels of the total endosulfan** found **in** the **farmers** were **significantly higher** than the mean level present in the non-occupationally exposed people group. The results obtained revealed that the pesticide could be detected practically intact in human blood, the similarity of the results obtained from the

		serum samples of the two studied groups and the differences found when the **urine samples** were analyzed seemed to **indicate** that urine analysis offers information about a **recent exposition** of the individual and serum analysis shows that information can be attributed to less recent expositions.
5.4	**Title :** **Oxidative stress responses in different organs of Jenynsia multidentata exposed to Endosulfan** **Authors and their affiliations:** M.L. Ballesterosa, D.A.Wunderlinb, M.A.Bistonia, a Universida Nacionalde Co´rdoba, Facult adde Ciencias Exacta sFı´sicasy Naturales,Ca´tedra DiversidadAnimalII,Avda.Ve´lez Sa´rsfield 299, 5000 Co´rdoba, Argentina b Universid Nacional deCo´rdoba-CONICET, Facultad de Ciencias Quı´micas, Dto.Bioquı´mica Clı´nica-CIBICI **Published in:** **Ecotoxicology and Environmental Safety 72 (2009) 199–205** 2008 ElsevierInc.Allrightsreserved	**Major Findings:** Our present results demonstrate that exposure to a sublethal concentration of **Endosulfan results in oxidative stress** in several organs of J. multidentata. The **brain** was the **most sensitive organ to oxidative damage.**

5.5	**Title :** **DNA Damage and Mutagenicity Induced by Endosulfan and Its Metabolites** **Authors and their affiliations:** MahimaBajpayee,1 AlokKumar Pandey,1 SabinaZaidi,2 JavedMusarrat,2 Devendra Parmar,1 NeerajMathur,3 PrahladKishore Seth,1 and AlokDhawan1* 1) Developmental Toxicology Division, Industrial Toxicology Research Centre, Lucknow-226001, India 2) Department of Microbiology, Faculty of Agricultural Sciences, Aligarh Muslim University, Aligarh-202002, India 3) Epidemiology Section, Industrial Toxicology Research Centre, Lucknow-226001, India **Published in:** **Environmental and Molecular Mutagenesis 47:682^692 (2006)** VVC 2006Wiley-Liss, Inc.	**Major Findings:** Endosulfan and metabolites may interact with DNA directly or through the production of ROS. In conclusion, the present study is the first to compare endosulfan with its isomers and metabolites for their ability to induce mutations in a conventional bacterial test system and to induce DNA damage in mammalian cells. Endosulfan, its isomers, and metabolites were positive in both the bacterial and mammalian cell systems

5.6	**Title :** **Selective induction of the CYP3A family by endosulfan and DNA-adduct formation in different hepatic and hepatoma cells** **Authors and their affiliations:** M. Dubois a, A. Pfohl-Leszkowicz ', I. De Waziers ', P. Kremers S* a Universit P de Litge. Lahorcrtoire de Chimie M:dicale, lnstitut de Pathologir, B35, Centre Hospitalier Unir~ersitaue. B-4000 Surf Tilman, Belgium h E.N.S.A.T.. Lahorrrtoire de Toxicologic et SCcuritr' Alimentaire. 145 Al,. de Muret. 31076 Toulouse. France ' Uniti de Rerherche de Biochirnie Pharmacologique et MPtabolique (INSERM U751. CHU Necker-Erzfant Malades. 156 rue de Vougirard. 75730 Paris Cedex 15. France **Published in:** **Environmental Toxicology and Pharmacology 1 (1996) 249-256**	**Major Findings:** This report clearly shows the **genotoxicity** of endosulfan. This chlorinated insecticide induces the formation of abundant DNA adducts in both fetal rat hepatocytes and Hep G2 cells. Endosulfan strongly correlated to the high induction of CYP3A gene expression. Endosulfan has a **major impact on the human liver** via induction of CYP3A4 and CYP3A7.

5.7	**Title:** **Exposure to mixtures of endosulfan and zineb induces apoptotic and necrotic cell death in SH-SY5Y neuroblastoma cells, in vitro** **Authors and their affiliations:** Zhenquan Jia1 and Hara P. Misra1,2,* 1 Department of Biomedical Sciences and Pathobiology, College of Veterinary Medicine, Virginia Polytechnic Institute and State University, Blacksburg, VA 24061, USA 2 Edward Via Virginia College of Osteopathic Medicine, Virginia Tech Corporate Research Center, 2265 Kraft Drive, Blacksburg, VA 24060, USA **Published in:** **JOURNAL OF APPLIED TOXICOLOGY** **J. Appl. Toxicol. 2007; 27: 434–446** **Published online 16 February 2007 in Wiley InterScience (www.interscience.wiley.com) DOI: 10.1002/jat.1218**	**Major Findings:** A number of epidemiological studies have demonstrated a strong association between the incidence of Parkinson's disease and pesticide exposure In conclusion, our results help to better characterize pesticide-induced neuroblastoma cell death. **Both zineb and endosulfan were found to induce cytotoxicity in SH-SY5Y cells via both apoptotic and necrotic pathways.** Together, with evidence provided in this study, it appears likely that endosulfan and zineb alone or in combination play a role in the cell death in an in vitro model system that may, at least in part, be involved in the **degeneration of dopaminergic neurons and may be relevant for the pathogenesis of some of these neurodegenerative diseases.**
5.8	**Title:** **Advantages of Human Hepatocyte-Derived Transformants Expressing a Series of Human Cytochrome P450 Isoforms for Genotoxicity Examination** **Authors and their affiliations:** Tsuneo Hashizume,* Sumie Yoshitomi,† Satoru Asahi,* Rieko Uematsu,* Shigeo Matsumura,* Fumio Chatani,* and Hiroaki Oda‡,1 *Development Research Center and †Discovery Research Center, Pharmaceutical	**Major Findings:** Endosulfan was found to induce MN through the CYP3A4-mediated pathway Endosulfan sulfate was the **genotoxic** metabolite to induce MN ; this metabolite was considered to be produced in the HepG2 transformant expressing human CYP3A4 by the treatment with b-endosulfan.

	Research Division, Takeda Pharmaceutical Company Limited, 17-85 , Jusohonmachi 2-chome, Yodogawa-ku, Osaka 532-8686, Japan; and ‡Laboratory of Nutritional Biochemistry, Nagoya University Graduate School of Bioagricultural Sciences, Furo-cho, Chikusa-ku, Nagoya 464-8601, Japan **Published in:** **TOXICOLOGICAL SCIENCES 116(2), 488–497 (2010) doi:10.1093/toxsci/kfq154**	
5.9	**Title:** **Citrinin and endosulfan induced teratogenic effects in Wistar rats** **Authors and their affiliations:** Nittin D. Singh,† Anil K. Sharma,* Prabhaker Dwivedi, Rajendra D. Patil and Manoj Kumar Division of Pathology, Indian Veterinary Research Institute, Izatnagar- 243122, India **Published in:** **JOURNAL OF APPLIED TOXICOLOGY** **J. Appl. Toxicol. 2007; 27: 143–151** **Published online 22 December 2006 in Wiley InterScience (www.interscience.wiley.com) DOI: 10.1002/jat.1185** 2006 John Wiley & Sons, Ltd	**Major Findings:** The present investigation was **conducted to evaluate the teratogenic potential of citrinin (CIT) and endosulfan** either alone or in combination in pregnant rats during gestational days 6–20. **In the present study, endosulfan treatment induced** **fetal gross anomalies The internal hydrocephalus, cerebellar hypoplasia, microphthalmia, contracted and notched kidneys, multilobulated liver, dilated renal pelvis, incomplete ossification of skull bones, rib anomalies and sacral and caudal vertebrae agenesis were the important fetal malformations** **The dose of endosulfan (1 mg kg–1 body weight)** **employed in the present study is lower than the dose established by the World Health Organization (WHO) for**

		reproductive toxicity assessment in rats (WHO, 1984). Because of widespread use or contamination of CIT and endosulfan in the environment and its occurrence in the animal and **human** food (Anderson, 1995) and the presence of residues in the blood and milk samples of females (Sancewicz-Pach et al., 1997; Sanghi et al., 2003**), these might pose a potential risk to developing fetuses during pre-natal and post-natal life**
5.10	**Title:** **Human health risk assessment of endosulfan. I: Toxicology and hazard identification** **Authors and their affiliations:** Marilyn H. Silva *, Sheryl L. Beauvais Department of Pesticide Regulation, California Environmental Protection Agency, Sacramento, CA 95812, USA **Published in:** **Regulatory Toxicology and Pharmacology 56 (2010) 4–17** 0273-2300/$ - see front matter Published by Elsevier Inc. doi:10.1016/j.yrtph.2009.08.013	**Major Findings:** **A primary risk assessment concern for endosulfan is that effects resulting from exposure during critical developmental stages (in utero, or to infants and children) will result in endocrine disruption and subsequent neurotoxicity, developmental or reproductive adverse effects that are irreversible.**

5.11	**Title:** **Genotoxicity evaluation of the insecticide endosulfan in the wetland macrophyte Bidens laevis L** **Authors and their affiliations:** De´bora J. Pe´rez a,b,c, Mirta L. Menone b,c,*, Elsa L. Camadro a,c, Vı´ctor J. Moreno b a) Laboratorio de Gene´tica, Estacio´n Experimental Agropecuaria Balcarce INTA e Facultad de Ciencias Agrarias e UNMdP,CC 276, 7620 Balcarce, Argentina b) Laboratorio de Ecotoxicologı´a, Departamento de Ciencias Marinas, Facultad de Ciencias Exactas y Naturales UNMdP, Funes 3350 (7600) Mar del Plata, Argentina c) Consejo Nacional de Investigaciones Cientı´ficas y Te´cnicas (CONICET), Rivadavia 1917, 1033, Buenos Aires, Argentina **Published in:** **Environmental Pollution 153 (2008) 695e698** _ 2007 Elsevier Ltd. All rights reserved.	**Major Findings:** The higher proportion of laggards and vagrand chromosomes observed at 5 mg/L would indicate that **endosulfan interacts with the spindle interrupting normal chromosome migration.** Endosulfan resulted genotoxic to B. laevis, a species of potential value for bioassays and in situ monitoring of environmental contamination by pesticides.
5.12	**Title:** **Genotoxicity evaluation of acute doses of endosulfan to freshwater teleost Channa punctatus (Bloch) by alkaline single-cell gel electrophoresis** **Authors and their affiliations:** Sanjay Pandey, N.S. Nagpure_, Ravindra Kumar, Shilpi Sharma, Satish K. Srivastava, Mahendra S. Verma	**Major Findings:** The Indian freshwater air-breathing teleost fish Channa punctatus (Bloch) was exposed to acute concentrations of the organochlorine pesticide **Endosulfan**. The presence of **DNA strand**

	National Bureau of Fish Genetics Resources, Indian council of Agriculture Research, Lucknow 226002, Uttar Pradesh, India **Published in:** **Ecotoxicology and Environmental Safety 65 (2006) 56–61** 2005 Elsevier Inc.	**breakage** in exposed specimens **indicated the genotoxic potential** of endosulfan.
5.13	**Title:** **Genotoxic Effects of a-Endosulfan and f3-Endosulfan on Human HepG2 Cells** **Authors and their affiliations:** Yuquan Lu,1 Kanehisa Morimoto,1 Tatsuya Takeshita,1 Toru Takeuchi,1 and Takeshi Saito2 1Department of Social and Environmental Medicine, Osaka University Graduate School of Medicine, Suita, Osaka, Japan; 2Laboratory of Environmental Biology, Department of Preventive Medicine, Hokkaido University School of Medicine, Sapporo, Japan **Published in:** Environmental Health Perspectives * VOLUME 108 1 NUMBER 6 1 June 2000	**Major Findings:** In this study, we examined the **genotoxicity** of endosulfan in vitro with a HepG2 cell line. After treating HepG2 cells with a- or 13-endosulfan for l hr, **DNA strand breaks were significantly induced** by a-endosulfan at concentrations fom 2 X 0o4 M to 1 x 10-3 M, and by ,-endosulfn at 1 x 10-3 M. The results of this study suggest that both endosulfan is **genotoxic** to HepG2 cells.
5.14	**Title:** **Micronucleus induction in erythrocytes of the Hyla pulchella tadpoles (Amphibia: Hylidae) exposed to insecticide endosulfan** **Authors and their affiliations:**	**Major Findings:** Results obtained here **showed a genotoxic effect of the endosulfan on erythrocytes** of H. puchella.

	Rafael C. Lajmanovich a,∗, Mariana Cabagna b, Paola M. Peltzer a, Gabriela A. Stringhini c, Andr´es M. Attademo c a National Council for Scientific and Technical Research (CONICET), Faculty of Biochemistry and Biological Sciences,FBCB-UNL, Pje. El Pozo s/n (3000), Santa Fe, Argentina b Cathedra of Normal Morphology, Faculty of Biochemistry and Biological Sciences, FBCB-UNL, Pje. El Pozo s/n (3000), Santa Fe, Argentina c High School of Health, Faculty of Biochemistry and Biological Sciences, EES-FBCB-UNL (3001), Santa Fe, Argentina **Published in:** **Mutation Research 587 (2005) 67–72** doi:10.1016/j.mrgentox.2005.08.001	It important noticed that commercial formulations of endosulfan utilized, contains many **'inert' ingredients** that can increase the toxicity of the product when compared to the technical-grade material. Furthermore, 'inert' ingredients used in formulated pesticide products are usually not disclosed and not included in most of the testing required in order to register these pesticides. Moreover, although 'inert' ingredients have no pesticide activity, they may be biologically active and sometimes the most toxic component of a pesticide formulation.
5.15	**Title:** **Effects of endosulfan on B cells of Langerhans islets in rat pancreas** **Authors and their affiliations:** Yusuf Kalender a,∗, Suna Kalender b, Meltem Uzunhisarcikli a, Ay¸se Ogutcu a, Fatma Açikgoz a, Dilek Durak c a Biology Department, Faculty of Arts and Science, Gazi University, 06500 Ankara, Turkey	**Major Findings:** **Chronic endosulfan administration for 2 months led to degenerative changes of various degrees of the pancreatic islets as well as the exocrine acini**. Insufficiency of insulin hormone causes the increase of blood glucose level at the end of the 5th and 6th weeks, blood glucose level significantly increased. This shows that B cells couldn't

	b Biology Department, Faculty of Education, Gazi University, 06500 Ankara, Turkey c Biology Department, Yozgat Faculty of Arts and Science, Erciyes University, Yozgat, Turkey **Published in:** **Toxicology 200 (2004) 205–211**	secrete adequate insulin Biochemical studies show that **endosulfan affects integral proteins and receptors of cell membrane.** In this study **endosulfan caused vacuoles and swelling of mitochondria.** Blood glucose levels and ultrastructural changes in this study show that **endosulfan affects B cells** of pancreas in rats even if it is **under the LD50 dose level**. Endosulfan not only has toxic effects on mammalian and other animals but it causes pollution as well. Therefore, microbial insecticides which are effective on target organisms and don't cause pollution should be used instead of endosulfan.
5.16	**Title:** **Effect of pesticides on estrogen receptor transactivation in vitro: A comparison of stable transfected MVLN and transient transfected MCF-7 cells** **Authors and their affiliations:** Eva C. Bonefeld-Jorgensen ∗, Heidi T. Gr¨unfeld, Irene M. Gjermandsen Unit of Environmental Biotechnology, Department of Environmental and Occupational Medicine, University of Aarhus, Vennelyst Boulevard 6, DK-8000 Aarhus, Denmark	**Major Findings:** The **estrogenic potential of four pesticides** (endosulfan, prochloraz, tolchlofos-methyl and propamocarb) was **compared** in parallel with 17_-estradiol (E2) by reporter constructs in transient transfected MCF-7BUS and in stable transfected MVLN cells. **In MVLN cells, endosulfan, prochloraz, tolchlofos-methyl and propamocarb caused cytotoxic responses at concentrations higher than 10,**

	Published in: **Molecular and Cellular Endocrinology 244 (2005) 20–30**	**25, 25 and 100 _M, respectively.**
5.17	**Title:** **Reactive oxygen species in in vitro pesticide-induced neuronal cell (SH-SY5Y) cytotoxicity: Role of NFκB and caspase-3** **Authors and their affiliations:** (SH-SY5Y) cytotoxicity: Role of NFκB and caspase-3 Zhenquan Jia, Hara P. Misra ◎ Edward Via Virginia College of Osteopathic Medicine, Virginia Tech Corporate Research Center, 2265 Kraft Drive, Blacksburg, VA 24060, USA **Published in:** **Free Radical Biology & Medicine 42 (2007) 288–298**	**Major Findings:** Our laboratory has demonstrated that **mice exposed to endosulfan (an organochlorine cyclodiene pesticide) and zineb (zinc ethylene bisdithiocarbamate (EBDC) fungicide) as juveniles and re-exposed at 8 months of age showed loss of dopamine (DA) in striatum. Mixtures of these pesticides also caused significantly increased levels of alphasynuclein, a major component of Lewy bodies and a hallmark of neurodegenerative diseases such as PD and Alzheimer's disease (AD).** In summary, the results of the present study demonstrate that neuronal cells (SH-SY5Y) exposed to endosulfan and zineb individually or in a mixture increase the production of hydrogen peroxide as well as superoxide anion, decrease SOD GPX, and CAT enzyme levels

		and increase lipid peroxide levels. This **holds tremendous implication** for the derivation of risk assessment guidelines for human exposure to pesticides.
5.18	**Title:** **Organochlorine pesticide residue levels and oxidative stress in preterm delivery cases** **Authors and their affiliations:** Rahul Pathak1, Sanvidhan G Suke1, Tanzeel Ahmed1, Rafat S Ahmed1, AK Tripathi1, Kiran Guleria2, CS Sharma3, SD Makhijani3 and BD Banerjee1 1) Environmental Biochemistry and Immunology laboratory, Department of Biochemistry, University College of Medical Sciences & G.T.B. Hospital (University of Delhi), Delhi, India 2) Department of Obstetrics and Gynecology, University College of Medical Sciences & G.T.B. Hospital (University of Delhi), Delhi, India 3) Instrumentation and Bio-Labs, Central Pollution Control Board, Ministry of Environment and Forest, Delhi, India **Published in:** **Human and Experimental Toxicology 29(5) 351–358**	**Major Findings:** The aim of the present study was to analyze the OCP residues in maternal and cord blood of women and assess the levels of different non-enzymatic oxidative stress markers as well as to establish correlation with OCP levels, if any. Levels of OCPs like Hexachlorocyclohexane (HCH), **endosulfan,** and DDT were analyzed by gas chromatography. Non-enzymatic oxidative stress was measured. In conclusion, our results suggest that higher levels of some of the OCP (like **Endosulfan**) **may be associated with Preterm Delivery and increased oxidative stress.**

5.19	**Title:** **HUMAN RED BLOOD CELL MEMBRANE DAMAGE BY ENDOSULFAN** **Authors and Affiliations:** CLIVE SUNIL DANIEL, SARITA AGARWAL and SHYAM S. AGARWAL *ICMR Centrefor Advanced Research in Genetics, Genetics Unit, Department of Medicine, K.G. Medical College, Lucknow (India)* **Published in:** **Toxicology Letters, 32 (1986) 113- 118**	**Major Points:** Endosulfan's in vitro toxicity on human red blood cell membrane was studied by staining with a fluorochrome dye, merocyanine-540 (MC-540) and Scanning Electron Microscopy (SEM). At a **concentration of 0.001 pg/ml (1 ppb) endosulfan was found to damage human red cell membranes** as demonstrated by fluorescence of 30-50% of red cells on staining with MC-540. At concentration of 1 pg/ml (1 ppm) the cells were markedly damaged.
5.20	**Title:** **Genotoxic evaluation of the insecticide endosulfan based on the induced GADD153-GFP reporter gene expression** **Authors and their affiliations** Li, Dahui, Liu, Jianzhang Li, Jianzhong College of Life Sciences, Graduate University of Chinese Academy of Sciences, Beijing, 100049, China. ldh_cas@yahoo.com.cn **Published in:** Environ Monit Assess. 2011 May;176(1-4):251-8. Epub 2010 Jul 14.	**Major Findings:** In this work, a genotoxic testing system has been developed based on the induction of a HepG2/GADD153-GFP reporter gene expression in response to the DNA-damaging agents. Methyl methanesulfonate, a known carcinogenic and genotoxic agent, was used to test the effects of damage dose and post-treatment incubation time on GADD153-GFP expression. Subsequently, the system was applied to the genotoxicity evaluation of endosulfan. **Endosulfan was able to cause the increase of GADD153-GFP expression at a sublethal dose** (0.02-20 mg/L). The results suggest that endosulfan has the

		potential genotoxicity for HepG2 cell line by inducing DNA damage.
5.21	**Title:** **Ameliorating effect of N-acetylcysteine and curcumin on pesticide-induced oxidative DNA damage in human peripheral blood mononuclear cells** **Authors and their affiliations** Ahmed, Tanzeel, Pathak, Rahul Mustafa, Md Kar, Rajarshi Tripathi, Ashok K, Ahmed, Rafat S, Banerjee B Environmental Biochemistry and Molecular Biology Laboratory, Department of Biochemistry, University College of Medical Sciences and G.T.B. Hospital (University of Delhi), Dilshad Garden, Delhi, 110 095, India. **Published in:** Environ Monit Assess. 2011 Aug;179(1-4):293-9. Epub 2010 Nov 4.	**Major Findings:** Subchronic exposure to endosulfan commonly affects the central nervous system, immune, gastrointestinal, renal, and reproductive system. This study was conducted to examine the role of oxidative stress in genotoxicity following pesticide exposure using human peripheral blood mononuclear cells (PBMC) in vitro. Further possible attenuation of genotoxicity was studied using N-acetylcysteine (NAC) and curcumin as known modulators of oxidative stress. Lipid peroxidation was assessed by cellular malondialdehyde (MDA) level and DNA damage was quantified by measuring 8-hydroxy-2'-deoxyguanosine (8-OH-dG) using ELISA. **The results indicate that pesticide-induced oxidative stress is probably responsible**

		for the DNA damage, and NAC or curcumin attenuate this effect by counteracting the oxidative stress.
5.22	**Title:** **Endosulfan-induced hepatotoxicity is route of exposure independent in rats** **Authors and their affiliations** Friday Effiong, Uboh Ekpo Nya, Asuquo Mbeh Ubana, Eteng Biochemistry Department, Faculty of Basic Medical Sciences, College of Medical Sciences, University of Calabar, Calabar, Nigeria. fridayuboh@yahoo.com. **Published in:** Toxicol Ind Health. 2011 Jul;27(6):483-8. Epub 2011 May 4.	**Major Findings:** **Endosulfan is an important hepatotoxic agent that generates free oxygen radicals in liver.** With the widespread use of endosulfan in agriculture, **human beings** are most likely to be exposed to it by eating food contaminated with endosulfan, exposure to its low levels by skin contact with contaminated soil, smoking cigarettes made from tobacco that has endosulfan residues on it, or by nose and whole body inhalation exposure in the farms during its application. **Since endosulfan is a frequently used pesticide, and the incidence of toxic injury to the liver tissue in relation to its widespread use reported in the literature, we considered it necessary to investigate whether endosulfan-induced liver injury could be route of exposure dependent.**

		The results of the enzyme and histological analyses showed that both oral and whole body inhalation exposure to endosulfan may cause liver tissue damage.

6) CARCINOGENCITY		
6.1	**Title:** Carcinogenic potential of endosulfan and its metabolites based on a quantum chemical model **Authors and their affiliations:** C.N.G. Bedor a,, R.J.L. Morais a, L.S. Cavalcanti a, J.V. Ferreira b, A.C. Pavão Universidade Federal do Vale do São Francisco, Av. José de Sá Maniçoba, S/N, Centro, 56304-205, Petrolina, PE, Brazil b Instituto Federal de Alagoas, Rua Mizael Domingues, 75, Poço, 57020-600, Maceió, AL, Brazil c Universidade Federal de Pernambuco, Av. Prof. Moraes Rego, 1235, Cidade Universitária, 50670-901, Recife, PE, Brazil **Published in:** **Science of the Total Environment 408 (2010) 6281–6284** 2010 Elsevier B.V. All rights reserved.	**Major Findings:** .The **aim** of the present study was **to investigate the carcinogenic potential of endosulfan** and its metabolites through electronic parameters that characterize the action of carcinogens, the **findings of the present study indicate that the use of this pesticide represents a risk to the health of the general population, especially rural workers.** The data from the present **study indicate that endosulfan and all its metabolites have carcinogenic potential**, based on the computational quantum chemical model. This places human health at risk, which is especially true for agriculture workers who are most exposed to this compound and therefore the most vulnerable.
6.2	**Title:** **Breast cancer risk and the combined effect of environmental estrogens** **Authors and their affiliations:** JesuI s M. Ibarluzea1, Mariana F. FernaIndez2, Loreto Santa-Marina1, Maria F. Olea-Serrano2, Ana M. Rivas2, Juan J. Aurrekoetxea1, JoseI ExpoI sito3, Miguel Lorenzo4, Pablo TorneI 5, Mercedes Villalobos6, Vicente Pedraza6, Annie J. Sasco7 & Nicolas Olea2,* 1Department of Health Guipuzkoa, San Sebastia´n, Basque Country, Spain; 2Laboratory of Medical Investigations,	**Major Findings:** The **estrogenicity of** adipose tissue extracts due to bioaccumulated **xenoestrogens** was associated with a **higher risk of breast cancer** in the leaner women, especially in the postmenopausal leaner group. Complex interactions between chemicals, endogenous or exogenous hormones and their natural ligands and receptors **may alter the internal homeostasis of** the estrogenic environment of

	Hospital Clı´nico University of Granada, Granada, Spain; 3Department of Oncology, Virgen de las Nieves University Hospital,m Granada, Spain; 4Department of Surgery, Torreca´rdenas Hospital, Almerı´a, Spain; **Published in:** **Cancer Causes and Control 15: 591–600, 2004. 591 _ 2004 Kluwer Academic Publishers. Printed in the Netherlands.**	**mammary tissue, leading to malignant transformation and cancer.**
6.3	**Title:** **Modulation of aromatase activity and mRNA by various selected pesticides in the human choriocarcinoma JEG-3 cell line** **Authors and their affiliations:** Nathalie Laville a, Patrick Balaguer b, Franc¸ois Brion a, Nathalie Hinfray a, Claude Casellas c, Jean-Marc Porcher a, S´elim A¨ıt-A¨ıssa a,∗ a INERIS, Ecotoxicological Risk Assessment Unit, BP 2, F-60550 Verneuil-en-Halatte, France b INSERM, U540, Molecular and Cellular Endocrinology of Cancers, F-34090 Montpellier, France c CNRS UMR 5569, University of Montpellier 1, BP 14 491, F-34093 Montpellier Cedex 5, France **Published in:** **Toxicology 228 (2006) 98–108** © 2006 Elsevier Ireland Ltd. All rights reserved.	**Major Findings:** Some pesticides may induce aromatase activity through transcriptional activation of the CYP19 gene When considering the physiologic consequences of the modulating effects on aromatase by pesticides, it is important to relate the present findings to the levels of human exposure We found out new **inducers of aromatase activity**, namely aldrin, chlordane, cypermethrine, methylparathion, **endosulfan**, methoxychlor, oxadiazon and metolachlor. The present study strengthens the view that **these chemicals** may contribute to the occurrence of **reproductive adverse effects in both human and aquatic organisms**.

6.4	**Title:** **Relation of Prediagnostic Serum Estrogen and Androgen Levels to Breast Cancer Risk.** **Authors and their affiliations:** CJoanne F. Dorgan,' Christopher Longcope, Hugh E. Stephenson, Jr., Roni T. Falk, Rosetta Miller, Charlene Franz, Lisa Kahle, William S. Campbell, Joseph A. Tangrea, and Arthur Schatzkin Division of Cancer Prevention and Control, National Cancer Institute,Bethesda. Maryland 20892-7326 Departments of Obstetrics and Gynecology and Medicine. University of Massachusetts Medical School, Worcester, Massachusetts 01655 **Published in:** **Cancer epidemiology biomarkers and prevention** **Cancer Epidemiol Biomarkers Prev 1996;5:533-539. Published online July 1, 1996.**	**Major Findings:** Results support the hypothesis that prediagnostic serum estrogens and **androgens are related to the subsequent diagnosis of breast cancer in postmenopausal woman**
6.5	**Title:** **The insecticide endosulfan and its two stereoisomers promote the growth of altered hepatic foci in rats** **Authors and their affiliations:** **Ronny Fransson-Steen1'2'3, Sten Flodstrdm1 and** **Lars WMrngard1** **'institute of Environmental Medicine, Karolinska Institutet, Box 60208, S-104 01 Stockholm and 2Department of Toxicology, Karolinska Institute*, Box 60400, S-104 01 Stockholm, Sweden** **Published in:** **Carcinogenesis vol.13 no. 12 pp.2299-**	**Major Findings:** Endosulfan was studied for its ability to act as a tumour promoter in a two-stage, altered hepatic foci bioassay in male Sprague-Dawley rats. The results show that endosulfan and its two stereoisomers promote the development of altered hepatic foci, suggesting that endosulfan is a tumour-promoting agent acting by clonal expansion of initiated cells. Our results show that the insecticide endosulfan is a

	23O3, 1992	potential liver tumour promoter in a similar manner to structurally-related chlorinated cyclodienes.
6.6	**Title:** **Effects of Pesticides on the Ratio of 160c/2- hydroxyestrone: A Biologic Marker of Breast Cancer Risk** **Authors and their affiliations:** H. Leon Bradlow,1 Devra Lee Davis,2 Gong Lin,1 Daniel Sepkovic,' and Raj Tiwari 1Strang-Cornell Cancer Research Laboratory, New York, New York; 20ffice of the Assistant Secretary for Health, Department of Health and Human Services, Washington, DC **Published in:** **Environ Health Perspect 103(Suppl 7):147-150 (1995)**	**Major Findings:** Xenobiotic estrogens are external compounds with estrogenic activity that may thereby affect the risk of breast cancer. **This paper describes a mechanism by which xenoestrogens may affect the development of breast cancer.** **These pesticides significantly increase the ratio of 16ct-OHE1/2-OHE, metabolites to values comparable to or greater than those observed after DMBA (the known rodent carcinogen 7,12-dimethylbenzyl anthracene (DMBA)).** The ratio of 16a-OHEl/2-OHEl may provide a marker for the risk of breast cancer.
6.7	**Title:** **Serum Sex Hormone Levels After Menopause and Subsequent Breast Cancer** **Authors and their affiliations:** F. Berrino, P. Muti, A. Micheli, V. Krogh, G. Secreto, Istituto Nazionale Tumori, Milan, Italy; G. Bolelli, Istituto di ClinicaOstetrica e Ginecologica "P Sfameni," Universita di Bologna, Italy; R. Sciajno, Istituto Nazionale Tumori, Milan, and Istituto di Clinica Ostetrica e Ginecologica "P Sfameni," Universita di Bologna; P. Pisani, Unit of Descriptive	**Major Findings:** In conclusion, this study has produced two important findings. First, in our population, **high levels of steroid sex hormones were found to be powerful predictors of breast cancer.** Second, although the association between breast cancer risk and testosterone levels was already known from case-control studies these results prospectively confirm this association.

	Epidemiology, International Agency for Research on Cancer, Lyon, France; S. Panico, Istituto di Medicina Intema e Malattie Dismetaboliche, Facolta di Medicina, Universita Federico II, Naples, Italy. **Published in:** **Journal of the National Cancer Institute. Vol. 88. No. 5. March 6, 1996**	
6.8	**Title:** **Estrogen Receptor Activation via Activation Function 2 Predicts Agonism of Xenoestrogens in Normal and Neoplastic Cells of the Uterine Myometrium** **Authors and Affiliations:** Deborah S. Hunter, Leslie C. Hodges, Peter M. Vonier, Robin Fuchs-Young, Marco M. Gottardis, and Cheryl L. Walker2 The University of Texas M. D. Anderson Cancer Center, Science Park Research Division, Smithville, Texas 78957 [D. S. H., L. C. H., R. F-Y., C. L. W.]; The Tulane-Xavier Center for Bioenvironmental Research, Tulane University, New Orleans, Louisiana 70112 [P. M. V.]; and Bristol Myers Squibb, Endocrine Oncology Pharmaceutical Research Institute, Princeton, New Jersey 08543 [M. M. G.] **Published in:** **CANCER RESEARCH 59, 3090–3099, July 1, 1999**	**Major Findings:** This report describes an in vitro/in vivo system for identifying the effects of Estrogen receptor ligands in the myometrium and elucidating their mechanism of action. The results suggest that some exogenous Estrogens (like endosulfan) may mimic the effects of endogenous estrogens on uterine leiomyoma and may contribute to a complex hormonal milieu that impacts both normal and neoplastic myometrium.

6.9	**Title:** **Prostate cancer risk and exposure to pesticides in British Columbia farmers** **Authors and their affiliations** Band, Pierre R, Abanto, Zenaida, Bert, Joel, Lang, Barbara, Fang, Raymond,Gallagher, Richard P, Le, Nhu D **Cancer Control Research, BC Cancer Agency, Vancouver, British Columbia, Canada.** **Published in:** Prostate. 2011 Feb 1;71(2):168-83. doi: 10.1002/pros.21232. Epub 2010 Aug 26.	**Major Findings:** Several epidemiologic studies have reported an increased risk of prostate cancer among farmers. Our aim was to assess the risk of developing prostate cancer in relation to exposure to specific active compounds in pesticides. A case-control approach was used with 1,516 prostate cancer patients and 4,994 age-matched internal controls. Conditional logistic regression was used to assess prostate cancer risk, adjusting for potential confounding variables and effect modifiers. **CONCLUSIONS: The significant association between prostate cancer risk and exposure to DDT, simazine , lindane, endosulfan, 2,4-D, 2,4-DB, and carbaryl.**

All the articles were reviewed and only relevant points were included in the synopsis.

This synopsis is not exhaustive and only forms a part of scientific evidences available in this office about the health effects of endosulfan.

Sd/

Dr. Mohammed Asheel
Asst. Nodal Officer

Endosulfan Rehabilitation Project