Farm Chemicals

THE EFFECTS OF INSECTICIDES AND HERBICIDES ON HEALTH

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Waters Center for Biological Medicine
The Effects of Insecticides and Herbicides on Health
The Effects of Insecticides and Herbicides on Health

• 100,000 new chemical compounds have been synthesized and released into our environment over the past 1 ½ centuries

• Far less than 1% have ever been tested for their effects on humans or other animals

• We know from the scientific literature that the effects of many toxins are multiplicative

\[ 1 + 1 + 1 \neq 3 \]

It may be 1,000,000!
Dr. Frederick vom Saal and his group at University of Missouri Endocrine Disruptors Group reviewed 700 studies revealing that the molecular action of the plasticizer **bis Phenol-A** is “essentially identical” in humans and animals.

“It is through these cell membrane receptors that **doses below a part per trillion** in cell culture can activate changes in cells.”

Reproductive Toxicology (July 27, 2007)
The Effects of Insecticides and Herbicides on Health

What is a “part per trillion”?

1 part per thousand → 1 drop in a shot glass
1 part per million → 1 drop in a 12 gallon fish tank
1 part per billion → 1 drop in 3 milk tanker trucks
1 part per trillion → 1 drop in 20 Olympic pools

0.05 mL

1 Olympic pool holds 660,430 gallons
The Effects of Insecticides and Herbicides on Health

Drs. Phillippe Grandjean and Philip Ladrigen - Neurotoxicologists

• There is a “silent epidemic” of brain diseases in children as a result of metals and chemicals contaminating our environment which represents an “uncontrolled experiment” on developing brains.

• Since 1950, the number of people with IQ’s over 130 has been cut in half as a result of this poisoning.

• Modern males are only “1/3 to ½” of men of a century ago in respect to their sperm counts as a result of this massive intoxication.
Sources of Toxic Chemicals

- Insecticides
- Weed killers
- Solvents
- Cleaning agents
- Soap
- Plastics
- Carpets, drapes, clothes
- Germicides
- Packaging materials
- Drugs
- Plants
- Food
- Water
- Air
- Industry
- Rodenticides
- Fungicides
Pesticides and Herbicides
- Organophosphates
- Pyrethrins
- 2,4-Dichlorophenoxyacetic acid (2, 4-D)
- Glyphosate
Organophosphate

- Ester of phosphoric acid
- Basis of most insecticides, herbicides, and nerve agents
Metabolism into DMP

Malathion

\[ 3\text{HCO} \quad \text{PSCHCH}_2\text{COOC}_2\text{H}_5 \]

Dimethylphosphate

\[ 3\text{HCO} \quad \text{P} \quad \text{O} \quad \text{O} \]

\[ 3\text{HCO} \quad \text{P} \quad \text{O} \quad \text{O} \]
Organophosphates (74) with Dimethylphosphate (DMP) Metabolite

- Methyl azinphos
- Methyl chlorpyrifos
- Dichlorvos
- Dicrotophos
- Dimethoate
- Fenitrothion
- Fenthion
- Methyl isazaphos
- Malathion

- Methidathion
- Methyl parathion
- Naled
- Methyl oxydemeton
- Phosmet
- Methyl pirimiphos
- Temephos
- Tetachlorvinphos
- Trichlorfon
“Absorbed through the lungs or skin or by eating them on food. Even at relatively low levels, organophosphates may be hazardous to human health.”


“The pesticides act on Acetylcholinesterase, an enzyme found in the brain chemicals closely related to those involved in ADHD, fetuses and young children, where brain development depends on a strict sequence of biological events, may be most at risk.”


“The United States Environmental Protection Agency lists parathion as a possible human carcinogen.[4]”


“Occupational organophosphate exposure is associated with an increased risk of Alzheimer's disease.[5]”

Exposure to Organophosphates Causes Chronic Illness

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Neuropsychiatric Evaluation in Subjects Chronically Exposed to Organophosphate Pesticides

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Long-term exposure to low levels of organophosphate pesticides (OP) may produce neuropsychiatric symptoms. We performed clinical, neuropsychiatric, and laboratory evaluations of 37 workers involved in family agriculture of tobacco from southern Brazil who had been exposed to OP for 3 months, and in 25 of these workers, after 3 months without exposure to OP. Plasma acetylcholinesterase activity levels of all subjects were within the normal range. Tobacco plantation use a combination of OP (chlorpyrifos and acephate), herbicides (glyphosate and clomazone), plant growth regulators (flumetralin), fungicides (iprodione), and insecticides (imidacloprid). Exposure to OP is known to induce clinical syndromes and biochemical alterations in humans. Besides acute cholinergic symptoms, which are related to the inhibition of acetylcholinesterase activity, acute or chronic OP exposure may cause clinical symptoms of OP poisoning in non-professional users and workers. The chronic effects of OP have been scarcely studied in exposed workers.
Pesticide-exposed children:

- Far less physical endurance in a test to see how long they could keep jumping up and down
- Inferior hand-eye coordination
- Could not draw a simple stick figure of a human being, which the non-exposed children could readily do.
• Children exposed to pesticides had more than twice the risk of developing pervasive developmental disorder (PDD)

• Children exposed to organophosphates had a 7x higher autism rate

• Pregnant Mothers exposed were more likely to have shorter pregnancies and their children had higher rate of impaired reflexes
Incidence of solid tumours among pesticide applicators exposed to the organophosphate insecticide diazinon in the Agricultural Health Study: an updated analysis.

Jones RR1, Barone-Adesi F2, Koutros S1, Lerro CC1, Blair A1, Lubin J1, Heltshe SL3, Hoppin JA4, Alavanja MC1, Beane Freeman LE1.

1Occupational and Environmental Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Department of Health and Human Services, Bethesda, Maryland, USA.

“We observed elevated lung cancer risks (N=283) among applicators with the greatest number of LT (RR=1.60; 95% CI 1.11 to 2.31; P(trend)=0.02) and IW days of diazinon use (RR=1.41; 95% CI 0.98 to 2.04; P(trend)=0.08).”

CONCLUSIONS:

“Our updated evaluation of diazinon provides additional evidence of an association with lung cancer risk. Newly identified links to kidney cancer and associations with aggressive prostate cancer require further evaluation.”
Organophosphate insecticide use and cancer incidence among spouses of pesticide applicators in the Agricultural Health Study.

OBJECTIVES:
Organophosphates (OPs) are among the most commonly used insecticides. OPs have been linked to cancer risk in some epidemiological studies, which have been largely conducted in predominantly male populations. We evaluated personal use of specific OPs and cancer incidence among female spouses of pesticide applicators in the prospective Agricultural Health Study cohort.

RESULTS:
Among 30,003 women, 25.9% reported OP use, and 718 OP-exposed women were diagnosed with cancer during the follow-up period. Any OP use was associated with an elevated risk of breast cancer (RR=1.20, 95% CI 1.01 to 1.43). Malathion, the most commonly reported OP, was associated with increased risk of thyroid cancer (RR=2.04, 95% CI 1.14 to 3.63) and decreased risk of non-Hodgkin lymphoma (RR=0.64, 95% CI 0.41 to 0.99). Diazinon use was associated with ovarian cancer (RR=1.87, 95% CI 1.02 to 3.43).

CONCLUSIONS:
We observed increased risk with OP use for several hormonally-related cancers, including breast, thyroid and ovary, suggesting potential for hormonally-mediated effects.
RESULTS:
A significant positive trend was seen for increasing incidence rate ratios (IRRs) by exposure quartiles of DMTP, DMDTP, DEP and DETP in XX18, YY18, XY18 and total disomy. A significant inverse association was observed between DMP and total disomy. Findings for total sum of DAP metabolites concealed individual associations as those results differed from the patterns observed for each individual metabolite.
Dose-response relationships appeared non-monotonic, with most of the increase in disomy rates occurring between the second and third exposure quartiles and without additional increases between the third and fourth exposure quartiles.

CONCLUSIONS:
This is the first epidemiologic study of this size to examine the relationship between environmental OP exposures and human sperm disomy outcomes. Our findings suggest that increased disomy rates were associated with specific DAP metabolites, suggesting that the impacts of OPs on testis function need further characterization in epidemiologic studies.
The goal of this study was to investigate the in vitro effects of methyl parathion (mPT) on cells in the oral cavity and evaluate the potential protective role of epigallocatechin-3-gallate (EGCG) on these effects.

Human gingival fibroblasts (HGF) were exposed to 10, 50, or 100 μg/ml mPT for 24 h and assessed for oxidative stress, as evidenced by reactive generation of oxygen species (ROS), induction of apoptotic cell death, DNA damage, and nitric oxide (NO) production.

Results showed that mPT produced significant oxidative stress, cytotoxicity, and genotoxicity and increased NO levels through stimulation of inducible NO synthase expression.

Finally, data demonstrated that EGCG (10, 25, or 50 μM) was able to inhibit the pesticide-induced effects on all parameters studied.
Pesticides and Parkinson's Disease-Is There a Link?

Terry P. Brown, Paul C. Rumsby, Alexander C. Capleton, Lesley Rushton and Leonard S. Levy

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Parkinson's disease (PD) is an idiopathic disease of the nervous system characterized by progressive tremor, bradykinesia, rigidity, and postural instability. It has been postulated that exogenous toxicants, including pesticides, might be involved in the etiology of PD. In this article we present a comprehensive review of the published epidemiologic and toxicologic literature and critically evaluate whether a relationship exists between pesticide exposure and PD. From the epidemiologic literature, there does appear to be a relatively consistent relationship between pesticide exposure and PD. This relationship appears strongest for exposure to herbicides and insecticides, and after long durations of exposure. Toxicologic data suggest that paraquat and rotenone may have neurotoxic actions that potentially play a role in the development of PD, with limited data for other pesticides. Development of PD, such as farming, rural living, and consumption of well water.

To date, there has been no comprehensive literature review of the epidemiologic and toxicologic evidence to critically evaluate whether a causal relationship exists between exposure to pesticides and the development of PD or parkinsonism. In this article we summarize such a critical review, undertaken on behalf of the U.K. Advisory Committee on Pesticides.
Pyrethrins - A Common Insecticide

ACTIVE INGREDIENTS:

- Pyrethrins: 5.00%
- * Piperonyl butoxide: 25.00%

OTHER INGREDIENTS: 70.00%

* (butylcarbityl) (6-propylpiperonyl) ether and related compounds

PYROCIDÉ®, MGK® - Registered trademarks of McLaughlin Gormley King Company
Pyrethrins - A Common Insecticide

- Toxin derived from a flower that targets the nervous system of insects
- One of the most commonly used pesticides
Pyrethrins - Modified From Nature

- Pyrethrum - crude extract of Chrysanthemum flower, toxic to humans and animals

![Pyrethrum Flower](image1)

- Pyrethroids - synthetic insecticidal chemicals with some chemical similarity to pyrethrin compounds, more toxic than pyrethrins
Pyrethrins - Metabolism

Permethrin → 3-phenoxystyrene → 3-PBA

Cyperpermethrin → 3-phenoxystyrene → 3-PBA

Deltamethrin → 3-phenoxystyrene → 3-PBA
2.2. Mechanism of insecticidal action

Pyrethroids are known to alter the normal function of insect nerves by modifying the kinetics of voltage-sensitive sodium channels, which mediate the transient increase in the sodium permeability of the nerve membrane that underlies the nerve action potential (Soderlund and Bloomquist, 1989; Bloomquist, 1993a).
Similar to insects, exposure to pyrethroids increases excitability in mammalian neurons by slowing the action potential falling phase.

Type I and type II pyrethroids delay mammalian VGSC inactivation resulting in a prolonged Na+ current.

The length of channel open time is dependent on the pyrethroid type, with type II pyrethroids holding VGSCs open much longer than type I.
Pyrethroids alter voltage gated sodium channels in insects and mammals.

**Figure 3.** The α subunit of the voltage-gated sodium channel. A. Schematic of VGSC α subunit indicating the four domains (I-IV) and their six transmembrane segments (1-6). The transmembrane segments and loop that form the channel pore are shown in green. The 4th transmembrane segment, shown in purple, acts as the voltage sensor. B. Four states of the VGSC. At resting membrane potentials the channel is closed. During the rising phase of an action potential the channel activates or opens. Channel inactivation contributes to the falling phase. During the undershoot phase the channel deactivates prior to returning to the closed phase once resting membrane resting potential has been restored. Modified from Motifolio Biomedical PowerPoint Toolkit Suite.
Pyrethroids increased the levels of some amino acid neurotransmitters and metabolites of monoamine neurotransmitters in the brain.

At doses that produced tremor in rats, permethrin increased:

- aspartate in the brainstem and striatum
- glutamate in the brain stem
- serotonin metabolite levels in the hypothalamus, brain stem, hippocampus, and brain stem
- dopamine metabolite levels in the striatum
Data are from 8–15 year old participants (N = 687) in the 2001–2002 NHANES.

Exposure was assessed using concurrent urinary levels of the pyrethroid metabolite 3-phenoxybenzoic acid (3-PBA).

Children with urinary 3-PBA above the limit of detection (LOD) were twice as likely to have ADHD compared with those below the LOD.

Hyperactive-impulsive symptoms increased by 50 % for every 10-fold increase in 3-PBA levels
2, 4-Dichlorophenoxyacetic Acid (2,4-D)

- One of the most commonly used herbicides
- One of the active ingredients of Agent Orange used in the Vietnam War
- Plant hormone that leads to uncontrolled growth in broadleaf plants
2,4-D (2,4-dichlorophenoxyacetic acid)

Not approved for use on lawns and gardens in Denmark, Norway, Kuwait and the Canadian provinces of Québec, and Ontario. Some forms banned in Australia.
Men who work with 2,4-D are at risk for abnormally shaped sperm and impaired fertility.

Increased risk of ALS among workers exposed to 2,4-D compared to other company employees

2,4-D interfered with myelination in the brain of animals as the result of lactational exposure changing behavior patterns of animals that included apathy, reduced social interaction, repetitive movements, tremors, and immobility in pups

Neuritis, weakness, nausea, abdominal pain, headache, dizziness, peripheral neuropathy, stupor, seizures, brain damage, and impaired reflexes have been associated with dermal or oral exposure.
Agent Orange and Heart Disease: Is There a Connection?

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HYPOTHYROIDISM AND PESTICIDE USE AMONG MALE PRIVATE PESTICIDE APPLICATORS IN THE AGRICULTURAL HEALTH STUDY

Whitney S. Goldner¹, Dale P. Sandler², Fang Yu³, Valerie Shostrom³, Jane A. Hoppin², Freya Kamel², and Tricia D. LeVan⁴,⁵
Glyphosate

Phosphate  glycine
The new compounds have a wide variety of uses such as chelating agents, wetting agents, biologically active compounds and as chemical intermediates for the production of amino-methylene-phosphonic acids and derivatives thereof.
Deficiency in trace elements like Mn, Cu, Zn, Se, Co, B, and Fe as well as macro elements like Mg, Ca, and others occur.

Deficiencies of these elements in diets, alone or in combination, are known to interfere with vital enzyme systems and cause disorders and diseases [29-31].

The Co and Mn levels were much too low in all animals for proper function and immune response (in comparison with reference levels).

This is a result of the strong chelating effect of glyphosate especially in chelating Co and Mn [30-32].

Correlations between glyphosate and blood serum parameters were significant for CK (R= 0.135), Se (R=-0.188) and Co (R= - 0.403) and Zn (R=0,175).

Correlations with the trace elements especially point to the influence of glyphosate on the health of cows.
REFERENCES:


Number of children (6-21yrs) with autism served by IDEA
plotted against glyphosate use on corn & soy (R = 0.9893, p <= 3.629e-07)
Sources: USDA:NASS; USDE:IDEA

Figure 23. Correlation between children with autism and glyphosate applications.
Glyphosate kills plants by interfering with the synthesis of the aromatic amino acids phenylalanine, tyrosine, and tryptophan.
Glyphosate occupies the binding site of phosphoenolpyruvate (PEP), inhibiting the EPSPS enzymes of different species of plants and microbes at different rates.
Glyphosate inhibits the EPSP synthase, which causes shikimate to accumulate in plant tissues and diverts energy and resources away from other processes.

Growth stops within hours of application it takes several days for the leaves to start to turn yellow.
EPSPS is produced only by plants and microbes; the gene coding for it is not in the mammalian genome.

**Gut flora of some animals contain EPSPS**
Glyphosate

Good and Bad Bacterial Flora

**GOOD**

- **BIFIDOBACTERIA**
  - The various strains help to regulate levels of other bacteria in the gut, modulate immune responses to invading pathogens, prevent tumour formation and produce vitamins.

**BAD**

- **CAMPYLOBACTER**
  - C. Jejuni and C. coli are the strains most commonly associated with human disease. Infection usually occurs through the ingestion of contaminated food.

**ESCHERICHIA COLI**
- Several types inhabit the human gut. They are involved in the production of vitamin K2 (essential for blood clotting) and help to keep bad bacteria in check. But some strains can lead to illness.

**LACTOBACILLI**
- Beneficial varieties produce vitamins and nutrients, boost immunity and protect against carcinogens.

**ENTEROCOCUS FAECALIS**
- A common cause of post-surgical infections.

**CLOSTRIDIUM DIFFICILE**
- Most harmful following a course of antibiotics when it is able to proliferate.
Abstract

Use of many pesticide products poses the problem of their effects on environment and health. Amongst them, the effects of **glyphosate** with its adjuvants and its by-products are regularly discussed. The aim of the present study was to shed light on the real impact on biodiversity and ecosystems of Roundup®), a major herbicide used worldwide, and the **glyphosate** it contains, by the study of their effects on growth and viability of microbial models, namely, on three food microorganisms (Geotrichum candidum, *Lactococcus lactis* subsp. cremoris and Lactobacillus delbrueckii subsp. bulgaricus) widely used as starters in traditional and industrial dairy technologies. The presented results evidence that Roundup® has an inhibitory effect on microbial growth and a microbicidal effect at lower concentrations than those recommended in agriculture.
Glyphosate, pathways to modern diseases II: Celiac sprue and gluten intolerance

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Republished study: long-term toxicity of a Roundup herbicide and a Roundup-tolerant genetically modified maize

Gilles-Eric Séralli ni*, Emilie Clair1, Robin Mesnage3, Steeve Gress1, Nicolas Defarge1, Manuela Malatesta7, Didier Hennequin3 and Joël Spiroux de Vendômois1

Abstract

Background: The health effects of a Roundup-tolerant NK603 genetically modified (GM) maize (from 11% in the diet), cultivated with or without Roundup application and Roundup alone (from 0.1 ppb of the full pesticide containing glyphosate and adjuvants) in drinking water, were evaluated for 2 years in rats. This study constitutes a follow-up investigation of a 90-day feeding study conducted by Monsanto in order to obtain commercial release of this GMO, employing the same rat strain and analyzing biochemical parameters on the same number of animals per group as our investigation. Our research represents the first chronic study on these substances, in which all observations including tumors are reported chronologically. Thus, it was not designed as a carcinogenicity study.
Most test done by the chemical companies which create these GMO products are run for 90 days.

Gilles-Eric Seralini conducted a study exactly replicating a Monsanto study from 8 years prior, however Seralini’s study lasted 2 years.

After 2 years, Seralini’s rats eating GMO corn had developed huge tumors.
• Females developed large mammary tumors
• Males presented up to four times more large, palpable tumors
Results

• Female rats had greater risk of mammary tumors
• Males had significantly increased of tumors of the liver and kidney.
• Sex hormone disruption for both genders.
• Enhanced oxidative stress
• Very significant kidney dysfunction
• Effects did not become apparent until after 4 months.

*G-E-Seralini et al. Env. Sciences Europe 2014: 26:14
GMO scientist Seralini vindicated in court ruling against defamatory fraud accusations; Forbes shill Henry Miller named as source of pro-Monsanto, anti-science lies

(NaturalNews) In a major victory for scientific truth, a high court in France has ruled that several false accusers, who made repeated efforts to destroy the work of Professor Gilles-Eric Seralini, engaged in defamation. And one of them is now being held legally responsible to pay the price for his crimes.

Marc Fellous, a former chairman at the Biomolecular Engineering Commission (BEC) in Paris, has officially been indicted for "forgery" and "the use of forgery" in defaming Prof. Seralini, whose work indicted Monsanto's Roundup herbicide and genetically-modified (GM) corn.

The BEC, which is responsible for approving genetically-modified organisms (GMOs) in France, had in its ranks a supposed leader who has now been exposed for forging the signature of a scientist in a dishonest attempt to discredit Prof. Seralini's work.
According to reports, Fellous forged this scientist's signature for the purpose of giving false credibility to claims that Prof. Seralini's work was incorrect, when in fact it was completely accurate. Prof. Seralini had previously been accused of conducting faulty science, but upon reassessment his work panned out as legitimate.

"The details of the case have not yet been publicly released but a source close to the case told GMWatch that Fellous had used or copied the signature of a scientist without his agreement to argue that Seralini and his co-researchers were wrong in their reassessment of Monsanto studies," reports GMOSeralini.org.

"The Seralini team's re-assessment reported finding signs of toxicity in the raw data from Monsanto's own rat feeding studies with GM maize. The sentence against Fellous has not yet been passed and is expected in June 2016."
Hospital Discharge Diagnoses of Breast Cancer & Glyphosate applied to corn & soy crops

R = 0.9375, p < 0.0001132

Sources: CDC; USDA
Glyphosate-Based Herbicides Produce Teratogenic Effects on Vertebrates by Impairing Retinoic Acid Signaling

Alejandra Paganelli, Victoria Gnazzo, Helena Acosta, Silvia L. López, and Andrés E. Carrasco*
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The broad spectrum herbicide glyphosate is widely used in agriculture worldwide. There has been ongoing controversy regarding the possible adverse effects of glyphosate on the environment and on human health. Reports of neural defects and craniofacial malformations from regions where glyphosate-based herbicides (GBH) are used led us to undertake an
Necrosis and apoptosis in testicular tissue resulted from 48 hour exposure to doses of Glyphosate formulations of 1 to 10,000 ppm.

Endocrine disruption was found to occur below the toxic dose.

1ppm Glyphosate decreased Testosterone levels 35%.
Toxicity of glyphosate-based pesticides to four North American frog species.

Howe CM, Berrill M, Pauli BD, Helbing CC, Werry K, Veldhoen N.

**Abstract**

Glyphosate-based herbicides are among the most widely used pesticides in the world. We compared the acute toxicity of the glyphosate end-use formulation Roundup Original to four North American amphibian species (Rana clamitans, R. pipiens, R. sylvatica, and Bufo americanus) and the toxicity of glyphosate technical, the polyethoxylated tallowamine surfactant (POEA) commonly used in glyphosate-based herbicides, and five newer glyphosate formulations to R. clamitans. For R. clamitans, acute toxicity values in order of decreasing toxicity were POEA > Roundup Original > Roundup Transorb > Glyphos AU; no significant acute toxicity was observed with glyphosate technical material or the glyphosate formulations Roundup Biactive, Touchdown, or Glyphos BIO. Comparisons between the four amphibian species showed that the toxicity of Roundup Original varied with species and developmental stage. Rana pipiens tadpoles chronically exposed to environmentally relevant concentrations of POEA or glyphosate formulations containing POEA showed decreased snout-vent length at metamorphosis and increased time to metamorphosis, tail damage, and gonadal abnormalities. These effects may be caused, in some part, by disruption of hormone signaling, because thyroid hormone receptor beta mRNA transcript levels were elevated by exposure to formulations containing glyphosate and POEA. Taken together, the data suggest that surfactant composition must be considered in the evaluation of toxicity of glyphosate-based herbicides.

- Toxicity of RoundUp Original varied depending on species and developmental age

- Toxicity in *R. clamitans*:
  
  POEA > RoundUp Original > RoundUp Transorb > Glyphos AU

- *R. pipiens* tadpoles exposed to POEA or glyphosate formulations with POEA negatively affected development via disruption of thyroid hormone receptor
In conclusion our study confirmed an association between exposure to phenoxyacetic acids and NHL [non-Hodgkin lymphoma] and the association with glyphosate was considerably strengthened.
“Initial reports about alleged biodegradability of glyphosate....turned out to be wrong”

Glyphosate remains in soil and spreads along with groundwater and it is detectable in low concentration in human body, where it:

• interferes with steroid hormone regulation
• impacts ROS formation and alters redox systems
• causes tissue necrosis and apoptosis

Formulations are more toxic than glyphosate alone.
Rats given 6 injections of Glyphosate over 2 weeks (50, 100, or 150 mg/kg)
• Repeated exposure caused immediate hypo-activity after each injection
• Hypo-activity was marked and lasted 2 days in rats receiving highest dose

Glyph decreased binding to Dopamine receptors in the Nucleus Accumbens (NAcc)

150 mg/kg decreased basal extracellular DA levels and induced DA release in striatum
Simultaneous exposure to multiple heavy metals and glyphosate may contribute to Sri Lankan agricultural nephropathy

Channa Jayasumana¹*, Sarath Gunatilake² and Sisira Siribaddana³

Abstract

Background: Sri Lankan Agricultural Nephropathy (SAN), a new form of chronic kidney disease among paddy farmers was first reported in 1994. It has now become the most debilitating public health issue in the dry zone of Sri Lanka. Previous studies showed SAN is a tubulo-interstitial type nephropathy and exposure to arsenic and cadmium may play a role in pathogenesis of the disease.

Methods: Urine samples of patients with SAN (N = 10) from Padavi-Sripura, a disease endemic area, and from two sets of controls, one from healthy participants (N = 10) from the same endemic area and the other from a non-endemic area (N = 10; Colombo district) were analyzed for 19 heavy metals and for the presence of the pesticide-glyphosate.

Results: In both cases and the controls who live in the endemic region, median concentrations of urinary Sb, As, Cd, Co, Pb, Mn, Ni, Ti and V exceed the reference range. With the exception of Mo in patients and Al, Cu, Mo, Se, Ti and Zn in endemic controls, creatinine adjusted values of urinary heavy metals and glyphosate were significantly higher when compared to non-endemic controls. Creatinine unadjusted values were significant higher for 14 of the 20 chemicals studied in endemic controls and 7 in patients, compared to non-endemic controls. The highest urinary glyphosate concentration was recorded in SAN patients (range 61.0-195.1 µg/g creatinine).

Conclusions: People in disease endemic area exposed to multiple heavy metals and glyphosate. Results are supportive of toxicological origin of SAN that is confined to specific geographical areas. Although we could not localize a single nephrotoxin as the culprit for SAN, multiple heavy metals and glyphosate may play a role in the pathogenesis. Heavy metals excessively present in the urine samples of patients with SAN are capable of causing damage to kidneys. Synergistic effects of multiple heavy metals and agrochemicals may be nephrotoxic.

Keywords: Chronic kidney disease, Heavy metals, Pesticides, Sri Lanka, Synergistic effect
Enlist Duo® herbicide

Twice as tough on problem weeds

Only Enlist Duo® herbicide with Colex-D® technology combines the proven performance of a new 2,4-D and glyphosate. The result: unrivaled weed control designed to land and stay on target.
• An evaluation of different cultivar maturity groups on different soil types, revealed a significant decrease in macro and micronutrients in leaf tissues, and in photosynthetic parameters (chlorophyll, photosynthetic rate, transpiration and stomatal conductance) with glyphosate use (single or sequential application).

• The lower biomass in GR soybeans compared to their isogenic normal lines probably represents additive effects from the decreased photosynthetic parameters as well as lower availability of nutrients in tissues of the glyphosate treated plants.
In March, 2015, 17 experts from 11 countries met at the International Agency for Research on Cancer (IARC; Lyon, France) to assess the carcinogenicity of the organophosphate pesticides tetrachlorvinphos, parathion, malathion, diazinon, and glyphosate (table). These assessments will be published as volume 112 of the IARC Monographs.\(^1\)
6.1 Cancer in humans
There is limited evidence in humans for the carcinogenicity of glyphosate. A positive association has been observed for non-Hodgkin lymphoma.

6.2 Cancer in experimental animals
There is sufficient evidence in experimental animals for the carcinogenicity of glyphosate.

6.3 Overall evaluation
Glyphosate is probably carcinogenic to humans (Groups 2A)
There is strong evidence that glyphosate can operate through two key characteristics of known human carcinogens, and that these can be operative in humans. Specifically:

- There is strong evidence that exposure to glyphosate or glyphosate-based formulations is genotoxic based on studies in humans in vitro and studies in experimental animals. One study in several communities in individuals exposed to glyphosate-based formulations also found chromosomal damage in blood cells; in this study, markers of chromosomal damage (micronucleus formation) were significantly greater after exposure than before exposure in the same individuals.

- There is strong evidence that glyphosate, glyphosate-based formulations, and aminomethylphosphonic acid can act to induce oxidative stress based on studies in experimental animals, and in studies in humans in vitro. This mechanism has been challenged experimentally by administering antioxidants, which abrogated the effects of glyphosate on oxidative stress. Studies in aquatic species provide additional evidence for glyphosate-induced oxidative stress.
The evaluation of these studies focused on the occurrence of Non-Hodgkin’s Lymphoma (NHL).

Overall, there is some evidence of a positive association between glyphosate exposure and risk of NHL from the case–control studies and the overall meta-analysis. However, it is notable that the only large cohort study of high quality found no evidence of an association at any exposure level. Glyphosate has been extensively tested for genotoxic effects using a variety of tests in a wide range of organisms.

The overall weight of evidence indicates that administration of glyphosate and its formulation products at doses as high as 2000 mg/kg body weight by the oral route, the route most relevant to human dietary exposure, was not associated with genotoxic effects in an overwhelming majority of studies conducted in mammals, a model considered to be appropriate for assessing genotoxic risks to humans.

The Meeting concluded that glyphosate is unlikely to be genotoxic at anticipated dietary exposures. Several carcinogenicity studies in mice and rats are available. The Meeting concluded that glyphosate is not carcinogenic in rats but could not exclude the possibility that it is carcinogenic in mice at very high doses.

In view of the absence of carcinogenic potential in rodents at human-relevant doses and the absence of genotoxicity by the oral route in mammals, and considering the epidemiological evidence from occupational exposures, the Meeting concluded that glyphosate is unlikely to pose a carcinogenic risk to humans from exposure through the diet.

The Meeting reaffirmed the group ADI for the sum of glyphosate and its metabolites of 0–1 mg/kg body weight on the basis of effects on the salivary gland. The Meeting concluded that it was not necessary to establish an ARfD for glyphosate or its metabolites in view of its low acute toxicity.
GPL-Toxic Screen

• 2,4D (2,4 Dichlorophenoxyacetic Acid)
  - Component of agent orange
  - Used in home lawn care and agriculture
• DMP (Dimethylphosphate)
• DEP (Diethylphosphate)
• 3PBA (3-Phenoxybutyric Acid)
  - Pyrethrin insecticide major metabolite
### Toxic Compounds

<table>
<thead>
<tr>
<th>Metabolite</th>
<th>Result mg/g creatinine</th>
<th>Percentile</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Herbicide</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2,4-Dichlorophenoxyacetic Acid (2,4-D)</td>
<td>0.80</td>
<td>LLOQ, 75th</td>
</tr>
<tr>
<td><strong>Pyrethroid Insecticide</strong></td>
<td></td>
<td>1.9</td>
</tr>
<tr>
<td>2,4-Dichlorophenoxyacetic Acid (2,4-D) is a very common herbicide that was a part of Agent Orange, which was used by the U.S. in the Vietnam War. It is most commonly used in agriculture on genetically modified foods, and as a weed killer for lawns. Exposure to 2,4-D via skin or oral ingestion is associated with neuritis, weakness, nausea, abdominal pain, headache, dizziness, peripheral neuropathy, stupor, seizures, brain damage, and impaired reflexes. 2,4-D is a known endocrine disruptor, and can block hormone distribution and cause glandular breakdown.</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Marker for Mitochondria Function</strong></td>
<td></td>
<td>5.8</td>
</tr>
<tr>
<td>Parent: Pyrethroids - Including Permethrin, Cypermethrin, Cyhalothrin, Fenpropathrin, Deltamethrin, Trihalomethrin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyrethrins are widely used as insecticides. Exposure during pregnancy doubles the likelihood of autism. Pyrethrins may affect neurological development, disrupt hormones, induce cancer, and suppress the immune system.</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Tiglyglycine (TG)</strong></td>
<td></td>
<td>LLOQ, 75th</td>
</tr>
<tr>
<td>Tiglyglycine (TG) is a marker for mitochondrial disorders resulting from mutations of mitochondrial DNA.</td>
<td></td>
<td>11, 14</td>
</tr>
</tbody>
</table>
Detoxification Methods

• Change to non-GMO organic food
• Exercise to develop sweating. Many chemicals are released in sweat. Use towel to remove sweat frequently since chemicals may be reabsorbed back into body.
• Use saunas to induce sweating. Hubbard protocol.
• Whole body massages with vegetable oil. Discard after use.
• Folate, B6, B12, TMG help PON enzyme eliminate toxic homocysteine thiolactone that decreases ability to detoxify pesticides
• Use oral or intravenous glutathione to remove many toxic chemicals. 500 mg per day oral.
• Drink purified water: distilled, reverse osmosis
Figure 2: Change in Symptom Severity with Detoxification

- Skin
- Cardiac
- Respiratory
- EENT
- Neurologic
- Emotional
- Cognitive
- Gastrointestinal
- Musculoskeletal
- Immunologic
The sum affect of a toxin is more than additive.

Interaction effects can be multiplicative, or exponential.

A fraction of a lethal dose of a chemical (when administered alone) may be lethal if there is an interaction effect with another toxin.

1 + 1 can equal 1,000.
1 + 1 can equal 1 million.
“A farm includes the passion of the farmer's heart, the interest of the farm's customers, the biological activity in the soil, the pleasantness of the air about the farm -- it's everything touching, emanating from, and supplying that piece of landscape. A farm is virtually a living organism.”

~ Joel Salatin