Glyphosate's Key Role in Chronic Kidney Disease of Unknown Origin

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MIT CSAIL
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Outline

• Overview
• Evidence of glyphosate exposure
• Glyphosate as a glycine analogue
• Glyphosate synergy through glycine substitution
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Overview
The Big Picture

• Agricultural workers in the rice paddies of Sri Lanka are dying in record numbers at a young age of a mysterious form of kidney failure called CKDu (Chronic Kidney Disease of Unknown Origin)
  – It appears to be due to a toxic exposure to the renal tubules
  – It is not linked to diabetes or high blood pressure
  – A similar disease confronts sugar cane workers in Central America called Mesoamerican Nephropathy (MeN)
• It has been proposed that excessive dehydration due to hard labor in the hot sun is a causal factor
• Others have pointed to toxic metals such as cadmium and arsenic in the well water they drink
• The workers are also exposed to toxic mold in their food
• They use both paraquat and glyphosate to control weeds in the paddies
Causes of CKDu

- Glyphosate 4+
- Paraquat dichloride 24% SL
- Arsenic
- Aluminum
- Cadmium
- Lead
- Mercury
Age Adjusted End Stage Renal Disease Deaths (ICD N18.0 & 585.6) plotted against %GE corn & soy planted ($R = 0.9578$, $p \leq 4.165e-06$) and glyphosate applied to corn & soy ($R = 0.9746$, $p \leq 7.244e-09$)

Sources: USDA:NASS; CDC

*Swanson et al., Journal of Organic Systems, 9(2), 2014*
Evidence of Glyphosate Exposure
Glyphosate & Paraquat Synergy*

“Simultaneous exposure of people to heavy metals and nephrotoxic pesticides may be a contributory factor in the pathogenesis and progression of CKDu.”

• Sri Lankans transitioned from paraquat to glyphosate to control weeds in rice paddies around the mid 1990’s
  – This was also when kidney failure first became evident

• 65% of test subjects tested positive for urinary glyphosate, and an additional 28% excreted AMPA (a breakdown product)

• High cadmium, arsenic and lead, along with low (depleted) selenium levels in well water

Drinking well water and occupational exposure to Herbicides is associated with chronic kidney disease, in Padavi-Sripura, Sri Lanka

Channa Jayasumana¹, Priyani Paranagama², Suneth Agampodi³, Chinthaka Wijewardane⁴, Sarath Gunatilake⁵ and Sisira Siribaddana⁶

• 5.3 million kg of glyphosate were imported into Sri Lanka in 2012
  – Over half of the total pesticides (herbicides, insecticides, fungicides)
• Male sex, farming and applying pesticides increase the risk of developing CKDu by almost three fold.
• Over 5-fold increased risk for those who had a history of drinking from abandoned wells
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More than 1 μg/L of glyphosate was found in 94% of recently abandoned wells and in 31% of currently active wells.
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FEBRUARY 21, 2019

With Monsanto and Glyphosate on the Run AAAS Revokes Award to Scientists Whose Studies Led to Ban on Weedkiller in Sri Lanka and Other Countries

by RUSSELL MOKHIBER
Lentils from Canada: High Glyphosate Contamination

Imported lentils laced with weed killer

S.N.V. SUDHIR I DC
VIJAYAWADA, JULY 18

Indians are consuming highly toxic lentils (masoor dal) and moong dal that are imported from Canada and Australia respectively. The lentils and moong dal are induced with the herbicide Glyphosate, which is being used by Canadian and Australian farmers indiscriminately to clear weeds.

Tests conducted by the Canadian Food Inspection Agency (CFIA) on thousands of samples of these lentils and moong dal grown by farmers in Canada and Australia found an average of 282 parts per billion (PPB) of glyphosate.

Tony Mitra

Farmers warned against using glyphosate without proper gear

DC CORRESPONDENT
VIJAYAWADA, JULY 18

Food safety and agricultural scientists are warning that the use of glyphosate may prove lethal. They are citing the example of Sri Lanka, where many sugarcane farmers died due to renal failure after being overexposed to the herbicide.

Glyphosate is a popular herbicide among farmers in the Telugu speaking states. Glyphosate is officially allowed to be used in only tea gardens, but is available across the country under various names and brands. "While farmers have to wear astronaut suit kind of gear while using glyphosate, it's not the case in countries such as India and Sri Lanka," said Mr. Tony Mitra, Indian born Canadian food security activist.

ActiveVIST FORCES CANADA TO TEST FOOD SAMPLES

Sri Lankan Red Lentil Dal Curry

India appears to import a lot of pulses from Canada, Italy and Myanmar. I've seen test results of Canadian grown pulses which are all desiccated by glyphosate. I also have seen test results of Australian grown pulses (known as moong dal in India) which also had 1000 parts per billion of glyphosate. "In Canada, in one of the provinces, some millions of acres of land is being used to grow pulses only to be exported to India," Mr. Mitra said.

He added that 87 per cent of Canadian lentils were contaminated and the average level of contamination was 282 parts per billion. Only 40 per cent of Indian samples were contaminated while the average was 25 parts per billion.

Food safety activists said every imported agriculture commodity needed to be tested for chemical residues but this was being ignored here. "While it is mandatory to label organic products, imported pulses are not labelled. It's very difficult to find out if we are consuming Canadian pulses or locally grown ones, if they are sold in loose. In some supermarkets, they label the country of origin where we will have a choice whether to buy the packet or not," said Dr. G.P. Ramanjaneyulu, agricultural scientist and founder, Centre for Sustainable Agriculture.

"At the entry points, these imported pulses are not being checked for glyphosate residue due to which pulses induce the highly toxic chemical for other countries are making their way into India and ultimately into the stomachs of Indians," he said.
Lentils imported from Canada are a popular food item in Sri Lanka.
Glyphosate as a Glycine Analogue
The Basics of Protein Synthesis

Template strand

DNA

RNA

Translation

Protein
What If Glyphosate Could Insert Itself Into Proteins during Synthesis???

-- Any proteins with conserved glycine residues are likely to be affected in a major way
Extra Piece Sticks Out at Active Site

Glyphosate

Alanine
Proline

glycine

Substrate no longer fits in active site
This explains how glyphosate disrupts EPSPS in the shikimate pathway: Multiple bacteria have developed resistance by replacing active site glycine with alanine and this is the basis for GMO Roundup Ready crops.*

*T Funke et al., Molecular basis for the herbicide resistance of Roundup Ready crops. PNAS 2006;103(35):13010-13015.
Inhibition of EPSPS by glyphosate: Resistant E. coli mutant

*Figure 3, S Eschenburg et al. Planta 2002;216:129-135.
Only Glyphosate Works!*  

“More than 1,000 analogs of glyphosate have been produced and tested for inhibition of EPSP synthase, but minor structural alterations typically resulted in dramatically reduced potency, and no compound superior to glyphosate was identified.”

Hypothesis:
These other molecules failed to work as an amino acid analogue of glycine, because they were not amino acids.

*T Funke et al. PNAS 2006; 103(35): 13010-13015.
Quote from Monsanto Study (1989)*

- Study exposed bluegill sunfish to carbon-14 radiolabelled glyphosate
- Measured radiolabel in tissues greatly exceeded measured glyphosate levels
- Proteolysis recovered more glyphosate
  - 20% yield → 70% yield

"Proteinase K hydrolyses proteins to amino acids and small oligopeptides, suggesting that a significant portion of the 14C activity residing in the bluegill sunfish tissue was tightly associated with or incorporated into protein."

Glyphosate Synergy Through Glycine Substitution
Glyphosate, Mesoamerican Nephropathy and Dehydration

• It has been widely proposed that dehydration due to overexertion under heat stress is a critical factor in Mesoamerican nephropathy*
  – Nocturia (frequent urination at night) is a commonly reported symptom
• Aquaporin is a protein that pumps water from the kidneys back into circulation in order to concentrate urine and protect from dehydration
• Aquaporin contains an essential glycine residue, and glyphosate substitution for this glycine would completely disrupt its ability to protect from water loss through the urine**

MATE1, Paraquat and Glyphosate

• MATE1 is a transport protein that pumps toxic chemicals from the renal tubules into the urine
• MATE1 has 32 glycine residues absolutely conserved among four species
• G64D mutation completely abolishes all transport activity (glycine to aspartate mutation)*
• This would cause paraquat to accumulate in the renal tubules
• Glyphosate substituting for G64 or any of the other highly conserved glycine residues would disrupt transport activity

Multidrug and Toxin Exclusion 1 (MATE1): exports paraquat into urine

Summary

• CKDu is a devastating kidney disease affecting young agricultural workers in Sri Lanka and Central America
• CKDu is a multifactorial disease with toxic metals, pesticides, heat stroke, nitrates and mold all playing a role
• Glyphosate works synergistically with the other factors to increase risk
• Glyphosate’s key mechanism of toxicity may be through its ability to substitute for glycine by mistake during protein synthesis
  – This has widespread consequences on various proteins throughout the body