Pesticides and CKDu Mesoamérica

Catharina Wesseling
Karolinska Institutet, Sweden
La Isla Network , USA

3rd International workshop on CKDu
San José, Costa Rica
March 2019

Review on pesticides and CKD presented at "2nd International Workshop on MeN"

Valcke et al., Environ Res, 2017

Reviewed studies ranked by their explanatory potential on the etiological role of pesticide for CKD/CKDu

Studies with low explanatory potential

Study	CKD marker	Potential to explain pesticide role in CKD/CKDu			Associations
		Low	Medium	High	
		Pesticide exposure indicator			
Rugama, 2001	CKD diagnosis at hospital admission	Pesticide use			Positive
Gracía-Trabanino et al., 2005	Proteinuria >15mg/L SCr >1.5 mg/dL	Pesticide use Pesticide use			No No
Torres-Lacourt et al. 2008	eGFR <60 ml/min1.73/m^2	Pesticide use Pesticide intoxication			Positive No
Peiris-John et al., 2006	Chronic renal failure diagnosis at hospital	Acetyl cholinesterase levels in four groups (exposed CRF, unexposed CRF, exposed non-CRF and unexposed non-CRF)			Positive
Wanigasuriya et al., 2007	CKDu hospital diagnosis	Pesticides			No
Aroonvilairat et al, 2015	BUN and SCr	Pesticide mixing and spraying in orchid for at least three months			No
Kamel & El Minshawy, 2010	ESRDu	Pesticide exposure			Positive

Studies with medium explanatory potential

Study	CKD marker	Potential to explain pesticide role in CKD/CKDu: Low	Medium	High	Associations
			Pesticide exposure indicator		
Sanoff et al., 2010	eGFR <60 ml/min/1.73m2		Pesticides		Weak positive
Orantes et al., 2011	Persistent CKD stages 1-5 determined twice with 3-months interval		Contact with agrichemicals		No
O'Donnell et al., 2011	eGFR <60 ml/min/1.73m2		Any pesticide exposure Mixing/applying pesticides		Weak positive No
Laux et al, 2012	Proteinuria		Work with pesticides		No
Raines et al., 2014	eGFR <60 ml/min/1.73m2		Lifetime days mixing/applying History of accidentally inhaling pesticides		No Posit, not interpretable
García-Trabanino et al., 2015	eGFR <60 ml/min/1.73m2		Any pesticide use Carbamate insecticides Glyphosate, paraquat, 2,4-D, triazines, organo-phosphates, pyrethroids		No Positive No
Laws et al, 2015 & 2016	Change in eGFR (ml/min/1.73m2) Change in early kidney injury markers		Job as pesticide applicator over 6-month period		No No
Wesseling et al., 2016	eGFR <80 ml/min/1.73m^2		Any pesticide use Glyphosate, paraquat, 2,4-D, chlorpyrifos, cypermethrin		No No
Wanigasuriya et al., 2011	Micro-proteinuria		Pesticides		No
Athuraliya *et al.*, 2011	Proteinuric CKD		Pesticides		No

Studies with high explanatory potential (none in Mesoamerica)

Study	CKD marker	Low	Medium	High	Associations
		Potential to explain pesticide role in CKD/CKDu			
				Pesticide exposure indicator	
Jayasumana et al., 2015	CKDu (according to criteria of Sri Lanka Ministry of Health)			Use of fertilizers, organo-phosphates, paraquat, MCPA, bispyribac, mancozeb Use of glyphosate Drinking water from serving wells and from abandoned wells (hardest water and highest glyphosate levels)	-Positive only in unadjusted analyses -Positive also in multivariate analyses -Positive with dose response
Siddharth et al, 2012 and 2014	CKDu with eGFR <60 ml/min/1.73m^2 for >3 months			Urinary organochlorine pesticides and metabolites and interaction with GST polymorphism	Positive
Lebov et al, 2016	ESRD among male applicators			Intensity weighted lifetime days for 39 pesticides: alachlor, atrazine, metalochlor, paraquat, pendimethalin, permethrin Petroleum oil, imazethapyr, coumaphos, parathion, phorate, aldicarb, chlordane, and metalaxyl Glyphosate and 24 other pesticides Pesticide exposure resulting in medical visit or hospitalization Diagnosed pesticide poisoning High level pesticide exposure event	Positive with dose-response Weak positive without dose-response No Positive No No
Lebov et al, 2015	ESRD among wives of licensed applicators			Intensity weighted lifetime days for applying -Pesticides in general -Specific pesticides Husband's use of paraquat Residential exposure	 Positive No Positive No

NIOSH study in El Salvador (Curwin et al, unpublished)

- In 2016 NIOSH investigators measured glyphosate and 2,4-D in the urine of sugarcane harvesters in El Salvador
- Only 21% of the samples were above the LOD.
- 20 of the 40 workers in the study had at least one of their samples above the LOD for glyphosate.

Glyphosate	N=40	am	pm
Min (ppm)	0.02	0.04	0.02
Max (ppm)	0.72	0.72	0.24
Avg (ppm)	0.08	0.13	0.07

2,4-D	N=40	am	pm
Min (ppm)	0.82	1.03	0.82
Max (ppm)	19.34	19.34	17
Avg (ppm)	4.17	5.40	3.72

Research with pesticide findings after 2015

- González-Quiroz et al: 2-year community cohort
  - 9.5% of men and 3.4 % of women showing a rapid decline of eGFR
  - 9.5% of men and no women had baseline dysfunction (≈ 60 ml/min/1.73m^2)
  - No associations with agrochemical use over last 6 months, self-reported at baseline (<30% among men for specific compounds)
    - Rapid decliners OR 1.70 (95% CI 0.72 to 4.03)
    - Baseline dysfunction OR 0.61 (95% CI 0.26 to 1.45)
    - Multilevel analysis with eGFR change during follow up, men: -1.25 ml/min/1.73m^2 (-3.20 to 0.67)
    - Glyphosate, paraquat, cypermethrin, methomyl: negative
- Smpokou et al, (see poster): nested case control
  - Pesticides or metabolites analyzed in urine: 2,4-D, glyphosate, MCPA, 4F-3PBA, 3-PBA, DCCA, CFCA, OH-PYR, TEB-OH, 5-OH-TBZ, ETU
  - Some pesticide metabolites were detected in urine in high levels (pyrethroids and chlorpyrifos)
  - No associations between pesticide residue levels and rapid decline in kidney function

Conclusions of review up to 2015 and after (1)

- Some evidence, more clearly in studies with stronger design and better exposure assessment
  - Evidence that certain pesticides produce acute and chronic kidney damage in humans
  - None of these studies was related to Mesoamerica and MeN
  - **No strong epidemiologic evidence that pesticides are the culprit of the CKDu epidemics.**
- Glyphosate in Sri Lanka an exception? No associations in other CKDu regions (or in Agricultural Health Study)
- 'Pesticide use' as exposure variable as unspecific as 'Food intake' in a nutritional study
  - Hundreds of active ingredients, heterogeneous toxicity profiles, heterogeneous use

Conclusions of review up to 2015 and after (2)

- **For a specific pesticide to be a key cause of an epidemic of the magnitude seen in Mesoamerica, Sri Lanka and India, it must be present during prolonged time periods in a diversity of agricultural settings in multiple countries, while generating elevated and widespread occupational or environmental exposures.**
- There is no research in CKDu endemic areas with a strong design and **examining the role of lifetime exposures to specific pesticides** or chemical groups with similar toxicological actions
  - Especially not in combination with heat exposure (or other risk factors).
- Given the diversity of pesticide use, such research is difficult and costly, but necessary to elucidate the role, if any, of agrochemicals in this epidemic.