Effects of paraquat on the neurodevelopment of the youngest of the young

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Abstract
In Suriname, the chemical paraquat is a widely used herbicide which is insufficiently regulated and controlled. In this short report we point out two main reasons for looking closer into the dangers paraquat may bring. First: paraquat is a common and very lethal method of attempting suicide. Second: serious suspicions exist that paraquat may influence young mothers and in particular the brains of their babies, even in the prenatal period, possibly leaving them with life-long damage in brain structure and function.

Key words: Paraquat use, paraquat exposure, suicide, pregnancy, neurodevelopmental consequences

Introduction
In Suriname, paraquat² is a frequently used herbicide. It is a quick-active, non-selective and rain-fast killer of plant tissue. Its use is for several reasons controversial. One of them concerns the suspected toxic effects on the health of animals and humans. In The European Union the application of paraquat is banned, in the Unites States only licensed applicators can purchase and use it³ and in Malaysia it was banned and later re-accepted because of its popularity. A second reason applies in particular to the fact that in upcoming, tropical agricultural countries paraquat is widely used as the main method in attempting suicide. Suriname, and the Nickerie district in particular is no exception to this, just like neighboring country Guyana: in almost one-third of suicide attempts paraquat is ingested and two-third of suicides happen by ingesting paraquat⁴. Like in many other developing world countries, paraquat, more known by one of its brand names Gramoxone, is widely used in Suriname for agricultural and non-agricultural weed control. Data from the Ministry of Agriculture and Fisheries show that in the period 2012-2015 on average each year 240000 liters paraquat have been imported (Department of Pesticides, Ministry of Agriculture and Fisheries, n.d.). Import and use of paraquat is not prohibited, the herbicide is for everyone easily accessible. Some rules on storage, selling, use and disposal exist, but both awareness and control are lacking. And like in many other developing and tropical countries paraquat is popular because of its effectiveness.

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² Chemical name: 1,1'-Dimethyl-4,4'-bipyridinium dichloride; CH3(C5H4N)2CH3Cl2.
³ The Court of First Instance of The European Communities, 2007.
⁴ See Harry et al., 2015; Balseiro, 2015; Graafsma et al., 2016.
This short report is not primarily devoted to the serious dangers paraquat may bring to suicidal people - in particular when impulsivity is high (Graafsma, 2016), but to another reason to reconsider accessibility to paraquat: suspicions that the herbicide may influence the health of mothers and their very young offspring.

Some general remarks on the toxic effects of paraquat on health

Ingestion of one teaspoon of paraquat (or 35mg/kg body weight) is fatal, leading to death within 30 days⁵. Through the bloodstream paraquat reaches all the areas of the body, with the lungs accumulating more paraquat. Higher concentrations of paraquat in the lungs then lead to lung damage. Damage of the liver and kidneys occurs while the kidneys try to remove the paraquat from the body. Inhalation of paraquat can lead to sore nose and throat and nose bleeding. Dermal exposure can lead to mild irritation, ulceration, blistering, desquamation (loosening of outer skin layer), necrosis (cell death in skin tissue) and second degree burns. Paraquat can also be absorbed through the skin. Contact with eyes can lead to eye irritation, inflamed eyelids and decreased visual acuity. The toxic concentration of paraquat in blood is between 0.06 and 0.32mg% (0.6 and 3.2 microgram/milliLiter). The lethal concentration is 1.5mg% (15mcg/mL) (Winek et al., 2001).⁶

Exposure during pregnancy

What we know by now is that paraquat can cross the placenta and enter the body of the foetus. Animal studies in the eighties showed that paraquat readily passes the placenta (Ingebrigtsen et al., 1984). The same applies to humans, as was shown for example by a study done in Taiwan. The study was done with nine pregnant women, who deliberately ingested paraquat. Paraquat concentrations were 2-6 times higher paraquat in the foetus than in the mother’s blood (Talbot et al., 1988).

A study on ten women with acute paraquat intoxication conducted in Greece also reported higher concentrations of paraquat in the placenta of the foetus than in the mother’s blood (Tsatsakis et al., 1996). Cases of foetal and neonatal deaths have been reported due to pesticide intoxication (Chomchai & Tialiwai, 2007); mostly caused by maternal poisoning (intentional and unintentional ingestion) and almost always fatal when happening before the third trimester. Therefore it generally is advised that pregnant women should not be exposed to paraquat.

What we in Suriname do not know exactly is: Firstly, do mothers know about, and comply with this advice? Do they protect themselves? And secondly, could it be that they are exposed to paraquat and other chemicals even if they avoid direct ingesting or using paraquat themselves? These questions are relevant because of the wide spread use of pesticides (agricultural practices, use in households etc.) and mercury (in gold mining), resulting in contamination of for example vegetables and fish. No research is available on the potential damage done to neutroceutical plants and leaves used in indigenous traditional medicine.

Paraquat exposure and child neurodevelopment

Infants can be exposed to paraquat in several ways. Most reported fatal cases are caused by accidental ingestion. Cases have been reported of toddlers sucking on a cleaned spray jet or bottle top, children confusing bottles for something drinkable or playing near paraquat spills (McDonagh & Martin, 1970; Wesseling et al., 2001). Ingestion through daily food is a second way. Paraquat residues have been found in fallen fruit on sprayed grass, in potatoes, onions, weeds and rice treated with paraquat. The residues are stable and degrade only slowly (JMPR, 2004). There is reason to be concerned here⁷.

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⁵ Less than 20mg/kg body weight is considered low dose, 20 to 40mg/kg bodyweight moderate dose and above 40mg/kg bodyweight high dose. See IPCS, 2000.

⁶ The concentration values are not absolute. They can be affected by differences in absorption route, sex, age, tolerance etc.

⁷ The Joint Meeting of the Food and Agriculture Organization (UN) Panel of Experts in Pesticide Residues in Food and the Environment and the WHO Core Assessment Group on Pesticide Residues (JMPR) estimated that the short-term dietary intake for children up to 6 years may be as high as 50% of the Acute Reference Dose of 0.006 mg/kg, and for the general population up to 20% (JMPR, 2004).
**Dermal exposure** is a third way. For example when children have skin contact with farmers work clothes, or contact with parents after they just have sprayed the fields, or when they are playing near sprayed fields or in the sprayed yard of the house. Data from the Surinamese Ministry of Agriculture and Fisheries suggest that in rural areas, at least 50% of households uses a herbicide to keep the yard clean (Department of Pesticides, Ministry of Agriculture and Fisheries, n.d.). It is popular because of its range (it kills all sorts of grasses and weeds), it acts fast and it is rain-fast within a couple of minutes.

Paraquat can enter the bloodstream through the skin. There are several case reports about paraquat and skin-contact in adults; paraquat causing skin burns and leading its way up to and damaging the lungs and kidneys (e.g. Tungsanga et al., 1983; Zhou et al., 2013)\(^8\). Even though the absorption/permeability of the infant’s skin doesn’t differ from adults, the crawling behavior and skin-versus-body weight ratio makes infants more vulnerable to dermal paraquat exposure (National Research Council, 1993).

Besides, many studies have accentuated acute exposure to high levels of paraquat and its damage to the lungs and kidneys. Often neglected however is the damage that may be caused by paraquat to the brain as a consequence of chronic exposure to low levels of paraquat (Dinis-Oliveira et al., 2006). We know that paraquat can cross the blood-brain barrier by binding to a neutral amino acid transporter and enter the brain cells, starting damaging chemical reactions there.

By now, it is suspected that exposure of the foetal brain to pesticides may cause chronic defects in the baby that might last a life time. Some authors suggest that especially exposure during critical periods in development (like in utero and in infancy) can result in permanent and progressive lesions or defects (Thiruchelvam et al., 2002). Paraquat is toxic mainly because of its redox cycle (for detailed information see Shimuzi et al., 2001; Dinis-Oliveira et al., 2006). It causes oxidative stress which then activates a cascade of reactions producing reactive oxygen species and as a consequence cellular damage (Castello et al., 2007; Dinis-Oliveira et al., 2006). Alarming messages - and yet research on the effect of paraquat on child neurodevelopment still is scarce.

However, a number of other environmental substances like lead, mercury and PCB’s (polychlorinated biphenyls) have extensively been studied and found to impair child development, even at low but continuous exposure levels (in particular during critical periods; for a review see Stein et al., 2002). Examples of impairment include problems with attention, memory, learning, social behavior and IQ. Although we do not know of studies that specifically address the effect of paraquat exposure on child neurodevelopment, there is reason for serious concern. That is because animal studies have shown that paraquat can impair motor- and cognitive function. In a study with mice for example, paraquat exposure was related to damage of neurons in the hippocampus (Mitra et al., 2011) and as a consequence impaired memory and learning (Chen et al., 2010).

Besides, a substantial number of animal studies reported damage from paraquat exposure in other regions in the brain resulting in impaired motor activity and defects in the “higher” cognitive functions like inhibition, planning and working memory - taken together in self-regulation (Brooks et al., 1999; Fahim et al., 2013; Fredriksson et al., 1993; Prasad et al., 2007).In conclusion for this part: the current state of affairs suggests that exposure to pesticides, paraquat included, during prenatal and post-natal development may be associated with neurodevelopmental deficits in young children.

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\(^8\) There is reason for serious concern here. Adults, even professionals from the government, spray paraquat, walking forwards right into the spray. They spray themselves continuously and in general - because of the heat - without the obligatory skin protection, without concern for the drift of paraquat through the air - and without sufficient awareness of the dangerous matter they handle.
But certainly, more research is needed to explore the effect of paraquat, especially its chronic exposure, on child neurodevelopment\(^9\).

**Recent developments in Suriname**

Acknowledging the importance of research, The Research Center of the Academic Hospital Paramaribo, Tulane University New Orleans and the Anton de Kom University of Suriname in 2015 started the Meki Tamara project.\(^{10}\) This project aims to assess the impact of exposure to heavy metals and pesticides on maternal and child health. The research team will follow 1000 pregnant women from seven regions of Suriname and the children of mothers with the highest and lowest exposures will be followed up for four years to assess their neuropsychological development.

Acknowledging the suspected toxic effects of widely used chemicals and the importance of preventive strategies, the Surinamese Ministry of Agriculture and Fisheries is working towards less toxic alternatives and advises the Surinamese population to limit the use of paraquat and other pesticide; e.g. by training various agricultural companies in pesticide usage and less toxic alternatives.\(^{11}\)

Instead of a complete ban on paraquat, the Surinamese government looks for a “restricted access” policy, like in the US, coupled with a gradual decrease of import quota and change to more environmental friendly ways of weed control.

More actions the Surinamese government is considering are:

- regulation of the import of pesticides, in particular from China. The idea is to channel all imports through ICAMA, the Chinese pesticide bureau, as to ensure quality and to avoid the import of mixed or contaminated products.
- introduction of farmers to Global GAP practices (Good Agricultural Production: regulation of food safety, protection of the environment and product quality) and licensing them.

**Conclusion**

In Suriname, the chemical paraquat is a widely used herbicide that is insufficiently regulated and controlled. In this short report we point out two main reasons for looking closer into the dangers paraquat may bring. First: paraquat is a common and very lethal method of attempting suicide. Second: serious suspicions exist that paraquat may influence young mothers and in particular the brains of their babies, even in the prenatal period, possibly leaving them with life-long damage in brain structure and function. It is therefore of great importance that citizens refrain from paraquat use for daily weed control and employers use paraquat with caution. Even more important is that we fully support the Meki Tamara project, and future projects, that assess the impact of exposure to pesticides on health.

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\(^9\) A major step forward is the Meki Tamara Study, recently undertaken by the ADEKUS Medical Faculty and Tulane University.

\(^{10}\) For details see the official website of the Research Center: www.researchcentersuriname.org

\(^{11}\) See the official website of the Ministry: http://www.gov.sr/ministerie-van-lv/waactueel

\(^{12}\) The Ministry expects to finish the needed legislation in 2017.
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