Adverse health effects caused by paraquat

A bibliography of documented evidence

Public Eye
PESTICIDE ACTION NETWORK UK
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For a just and pesticide-free future

IMPRINT Poisoning and adverse health effects caused by paraquat among agricultural workers and the public – A bibliography of documented evidence – February 2017 | **PUBLISHERS** Public Eye, Pesticide Action Network UK and Pesticide Action Network Asia-Pacific | **COMPILED BY** RICHARD ISENRING | **WITH ACKNOWLEDGEMENT TO** Barbara Dinham, François Meienberg, Laurent Gaberell and Stephanie Williamson | **PHOTO COVER** © Adobe Stock | **LAYOUT** Karin Hutter

Foreword by the publishers

In 1985, the Pesticide Action Network launched the global Dirty Dozen Campaign. It was the first global effort of PAN International to take action on some of the most harmful pesticides – including paraquat. Fourteen years ago, the Berne Declaration (today Public Eye) launched its campaign calling for Syngenta to stop selling its herbicide paraquat. Paraquat is now banned in over 40 countries, including in the European Union and Switzerland, Syngenta's home country, because of its adverse health effects. Paraquat was recently banned in Serbia, South Korea, Togo and Zimbabwe. In March 2016, the US Environmental Protection Agency announced its proposal to further restrict the use of paraquat and, among other measures, prohibit application from hand-held and backpack equipment as well as to restrict the use to certified pesticide applicators only. In addition, many labelling organisations such as the Fair Trade International, the Forest Stewardship Council, the Rainforest Alliance, and food corporations like Chiquita, or retailers like Migros and Coop in Switzerland, have all voluntarily prohibited paraquat.

Yet paraquat is still the third most widely used herbicide in the world. Syngenta continues to sell it in many developing countries, where its safe use has proven to be impossible. And still too many people die – or are severly injured – each year because of paraquat poisoning. Paraquat is highly toxic and there is no antidote. One small accidental sip can be fatal. Paraquat is about 28 times more acutely toxic than glyphosate. Acute poisoning may occur through contact with skin, eyes, or via inhalation. There is now also increasing evidence that chronic exposure to paraquat is linked with adverse effects, for example, on the respiratory system, in reproductive problems, and increased risk for Parkinson's disease. Agricultural workers and farmers are regularly exposed to this toxic substance during handling and mixing, spraying and working in recently sprayed fields.

As the UN's Food & Agriculture Organisation has demonstrated, training in proper pesticide use is not a solution for risks associated with the use of highly hazardous products such as paraquat. Users in developing countries often do not have access to the required Personal Protective Equipment (PPE). Moreover, expecting users to wear full protective clothing in warm and humid climates is unrealistic. And even in the European Union, where PPE is widely available and used, paraquat was considered too dangerous for users and therefore banned.

Safe use of paraquat in developing countries is simply not happening on the ground. We have provided numerous reports with evidence of that. Just to mention our latest reports, in 2015 we published together with a NGO coalition two reports[1] on conditions of paraquat

use in India in which we documented that: most workers and farmers apply paraquat without any personal protective equipment and have never received any training; in some places paraquat is sold in plastic carrying bags; many users cannot read the label; it is mixed with other ingredients that are not recommended; it is sprayed with leaking knapsack sprayers; it is applied on crops for which its use has not been approved; and containers are re-used for drinking water.

This literature review updates the scientific information provided in the report *Paraquat, Unacceptable risks for users,* published by the Berne Declaration, Pesticide Action Network Asia Pacific and Pesticide Action Network UK in its third edition in 2011[2]. Therefore this report provides first of all an update on literature published since 2011. While older studies referenced in the 2011 report are not mentioned again, several studies published before 2011 but not cited in the 2011 report are now included.

We would like to warmly thank the author of this report, Richard Isenring, for his excellent work and commitment and especially Barbara Dinham for her active support. As this new report shows, evidence of the negative health effects of paraquat and its link with chronic diseases, such as Parkinson's disease or cancer is increasing. This report also clearly documents the positive health effects in countries that have implemented a ban on paraquat, or stricter regulations. As the report clearly shows, the case for a global phase out of paraquat is stronger today than ever.

Laurent Gaberell, Public Eye, Sarojeni Rengam, PANAP, and Stephanie Williamson, PAN UK, February 2017

Summary:
Adverse health effects caused by paraquat

Paraquat is *very toxic* to workers applying the chemical, on an acute basis. In many countries paraquat remains the pesticide active ingredient responsible for more fatal poisonings than any other pesticide substance. The EU has *banned* paraquat as the potential exposure of workers is considered too high. Even when workers wear personal protective equipment (PPE) as required, exposure to pesticides during spraying cannot be eliminated. Eye injuries from spill or splashes can result in impaired sight. Exposure of skin to the diluted product or concentrate will cause irritation or skin burn and this leads to an increased absorption. Exposure can also occur through inhalation or ingestion. No antidote is available.

Chronic exposure can have adverse effects on the respiratory system, e.g. reduced lung function. Workers who are exposed to paraquat over a longer period have been found to be at an increased risk of developing Parkinson's disease later in life. Paraquat has endocrine and immunotoxic effects. In epidemiological studies paraquat exposure was associated with increased incidence of leukaemia, lymphoma, skin and brain cancer.

Toxicologists have questioned the World Health Organisation (WHO) categorization of paraquat as WHO Class II ('Moderately hazardous') and have argued that *"it would be appropriate to assign paraquat to class I"* (Nagami et al 2005). Dawson et al (2010) emphasize that human toxicity data should be incorporated into regulatory decisions and the WHO's toxicity scheme and have urged the WHO to immediately reclassify certain pesticide formulations, including paraquat, which are several times more lethal than other pesticides in the same chemical class or functional type. The Chemical Review Committee for the Rotterdam (PIC) Convention categorizes all liquid concentrates of paraquat ion at or above 200 g/L (corresponding to paraquat dichloride ≥ 276 g/L) as *'Severely Hazardous Pesticide Formulation'*. However, these are the most common concentrations sold. Agricultural workers have to dilute the concentrate, mix and load the spray solution.

In developing countries reported occupational and non-intentional poisonings vary from 10 % to 50 % (WHO 2004; cited by Thundiyil et al 2004). For example, in the Central American isthmus (Belize, Costa Rica, El Salvador, Guatemala, Honduras, Nicaragua and Panama), over one third (36 %) of acute poisonings with various pesticides were occupational in 2000, followed by intentional and accidental poisonings (Henao & Arbelaez 2002). Additionally, a very high number of pesticide occupational poisonings are not reported, especially those occurring in rural areas. Although the available data is limited, a large proportion of paraquat poisonings occurs from accidental intake and through occupational exposure. For example, in Burkina Faso, of 922 pesticide poisoning cases reported between 2002 and 2010, 53 % were non-intentional, and 19 % occurred during agricultural work (UNEP & FAO 2010).

Instructions on the product label can be difficult to understand and may be inadequate. In many countries the necessary protection is not available or affordable. In hot and humid climates it is difficult or impracticable to wear the correct PPE. A FAO study in Burkina Faso (2010) found that less than 1 % of farmers use the personal protective equipment recommended. Another study in Ghana found that virtually no farmers use all the recommended equipment (NPAS 2012). Such conditions easily lead to acute paraquat poisoning via occupational exposure.

In several countries paraquat has been misused for suicide, or self-harm, causing such high numbers of fatalities that it has been banned or severely restricted. Approaches aimed at improved safety, such as new formulations and recommendations for safer storage, have had limited impact. Of 250 patients who attempted suicide by drinking paraquat in South Korea in 2007 only 38 % had chosen this particular pesticide knowingly, while two of three patients ingested paraquat merely as it was available at the time (Seok et al 2009).

Studies observed that suicides decreased significantly in South Korea after paraquat was banned, and many medical experts support its prohibition as a preventive strategy (Cha et al 2015; Lee et al 2015; Lin et al 2006; Myung et al 2015).

Implementing bans – or stricter regulations – of paraquat has proven successful to reduce not only cases related to self harm but also occupational, accidental and unintentional cases. A decrease of paraquat poisoning was noted in the EU after the ban was introduced (Cassidy et al 2012). Stricter regulation and enforcement led to a decrease in paraquat poisonnings in Japan (Ito & Nakamura 2008). In Malaysia, after the ban of paraquat was lifted in 2007 there was a marked increase in the number of cases relating to paraquat exposure (Sazaroni et al 2012; Tan et al 2013). Restricting access to lethal methods such as toxic pesticides and firearms has proven to substantially reduce the

number of suicide deaths (Barber et al 2014; Mann et al 2005). The WHO has recommended this measure (WHO 2014).

Even when workers use protective equipment as required, exposure during mixing of solutions and spraying cannot be eliminated. In view of the very high acute toxicity of paraquat, its ability to damage skin and be absorbed via skin, absence of an antidote, and chronic health risk, in particular for Parkinson's disease, and as a sufficient protection level for workers cannot be reached even under conditions of "normal use", the control of paraquat under the Rotterdam PIC Convention as a first step is urgently warranted.

Surveillance of poisonings and regulatory control of pesticides need to be strongly improved in most countries. National policies must be implemented to protect agricultural workers and provide effective guidance for pesticide use. In the USA, numerous accidental paraquat poisonings have been reported, many of these fatal and often as paraquat was transferred to a drink container (contrary to use directions). Dermal exposure to paraquat during application – via leaks or spills and contamination of skin while spraying – is common and has resulted in severe skin burns that can necessitate skin graft, eye injuries, and several fatalities (Fortenberry et al 2016).[3] Therefore the US Environmental Protection Agency proposed to prohibit all handheld application equipment, including backpack sprayers and hand gun sprayers, for paraquat dichloride, and proposes restricting use of paraquat to certified applicators only and also requiring that all paraquat containers use closed system technology (EPA 2016).[4]

At the international level FAO's Code of Conduct is calling on countries to identify highly hazardous pesticides that cause severe or irreversible harm to human health under normal conditions of use, and to remove them from the market (FAO & WHO 2014).[5] The PIC Convention requires reporting of poisonings involving severely hazardous pesticide formulations such as paraquat (at concentrations of 20% or above) (UNEP 2004).[6] Paraquat continues to cause a very high number of deaths globally, due both to accidental exposure and self harm, and the risks from using it under actual working conditions are extremely high. As many of the scientific studies referenced in this report recommend, a global ban of paraquat seems to be the only effective measure in order to avoid the continued poisoning of agricultural workers and farmers.

Smallholder farmer mixing and spraying paraquat, without adequate protection (Pakistan) | © Marion Nitsch

1 Occupational and accidental exposure to paraquat

1.1 – SYNOPSIS: ACUTE HEALTH EFFECTS

Although paraquat has now been used on a global scale for over 50 years and has caused innumerable fatal poisonings, both deliberate and unintentional, there is still no effective treatment (Gawarammana & Buckley 2011; Gil et al 2014; Peng et al 2012; Simões et al 2012). Dinis-Oliveira et al 2009 pointed out that *"the currently used therapeutic flowchart needs to be refined, since neither the accumulation, nor the injuries related to PQ [paraquat] exposure seem to be effectively reverted."* (p.12) So far it has also not been shown that formulations of paraquat which claim to present lower poisoning risks are any less toxic or offer more treatment options (Bateman 2008; Baltazar et al 2013). Paraquat poisonings are generally more frequent in rural areas where access to the necessary emergency treatment is limited. A reliable diagnosis and prognosis will require advanced analytical methods. Urine tests for paraquat, although simpler than analyzing blood, have a low sensitivity and can give repeated false negative results even in case of poisoning (Monteiro et al 2011). However, some patients with low paraquat levels may also die (Gil et al 2014). With pesticides, early treatment is less likely than with other poisons with a slower action. This contributes to the high proportion of fatal pesticide-related poisonings in rural areas, besides easy access to highly poisonous products and the frequently lacking medical facilities (Bose et al 2009). Even where poisonings did not result from deliberate ingestion for self-harm, pesticides, and paraquat in particular, generally resulted in the highest fatality rates (Rajasuriar et al 2007; Yu et al 2015; Zhang et al 2013).

Several authors have reported absorption of paraquat solution through intact skin which resulted in systemic poisoning (Premaratna & Rathnasena 2008; Soloukides et al 2007; Zhou et al 2013). Paraquat poisoning has occurred during the application of the diluted product, e.g. in South Korea and Burkina Faso (Lee et al 2012; Toe et al 2013). Therefore the Chemical Review Committee of the Rotterdam Convention recommended to list products with 20 % or more of paraquat ion as *"Severely Hazardous Pesticide Formulation"* (UNEP 2012).[7] This decision was based on the finding that between 1996 and 2010 in Burkina Faso 53 farmers had suffered adverse health effects after occupational exposure to paraquat. At least 26 of these cases needed medical treatment, and a minimum of 11 hospitalizations were required, while treatment was unknown in 16 cases (UNEP 2012, Decision Guidance Document). Adverse effects included clear symptoms of acute poisoning. Farmers wore limited protective clothing as this was considered too expensive or was not available locally.

Several studies found that paraquat, and a number of other pesticides, both trigger and exacerbate attacks of those with allergic asthma. Similar to organophosphates, studies found that exposure to paraquat and particularly subsequent poisoning events were associated with an increased risk of depression (Kim et al 2013). In Malaysia numbers of paraquat poisonings have been increasing again after a previous ban was lifted in 2007 (Sazaron et al 2012).

In Iran, about one quarter of paraquat poisonings treated at two hospitals in Shiraz were accidental (Goudarzi et al 2014). An Iranian farmer who had been accidentally sprayed in the face with dilute paraquat solution later developed severe lung fibrosis, although he vomited up the ingested solution, and one lung had to be removed (Davarpanah et al 2015). Measuring paraquat levels in blood is critical to clinical evaluation (Shi et al 2012). But many hospitals or medical centers do not have the necessary equipment or resources, especially in rural areas.

Paraquat is among five pesticides most frequently used in Plateau State, Nigeria. Due to lacking knowledge or literacy pesticides are often not used properly in Nigeria. This has resulted in fatal poisonings of farmers with paraquat and threatens public health (Gushit et al 2013). While paraquat appears to be no longer approved for use on cocoa in Nigeria, stocks of banned pesticides continue to be sold and used (Mokwunye et al 2014). In Ghana paraquat use under inadequate conditions poses a major risk to farmers and the public (NPAS 2012).

Medical experts have called for a global ban or effective restrictions on the availability of paraquat as its ingestion causes irreversible effects, which increases the likelihood of fatal outcome when vulnerable persons impulsively ingest this dangerous poison.

Accidental paraquat poisoning of children is a serious problem in many countries (Ge 2013; Kafkala et al 2015; Lee et al 2014; Zhang et al 2013). Both children and older persons are more vulnerable to pesticide poisoning (Yu et al 2015). In China

the incidence of paraquat poisoning is increasing and accidental exposure to paraquat occurred predominantly in younger children under ten years (Duan & Wang 2016). PAN Asia Pacific emphasizes the urgency to protect children and young (underage) farmers from exposure to pesticides. Fatal poisoning has occurred after accidentally ingesting as little as one sip of paraquat solution (Wong et al 2006).

In the USA, numbers of unintentional poisonings with paraquat are high; occupational and accidental cases accounted for about 75 % of all paraquat posisonings between 2010 and 2015 (AAPCC). Paraquat and diquat caused the majority (85 %) of all herbicide-related deaths in the USA (Fortenberry et al 2016). Medical experts demanded that the maximum concentration of paraquat formulations should be reduced to 5 % in the USA (Ford 2013; Geller 2013). In Japan such a reduction was not effective as the mortality rate of paraquat poisoning has remained about 80 %, even with 5 % products early as 1985, the Japanese Association of Rural Medicine adopted a resolution against the use of paraquat and demanded strict controls of its sale (Nagami et al 2010).

The WHO recommends legislation to remove locally problematic pesticides from agricultural practice, as well as reducing toxicity of pesticides (WHO 2014). Even then, restrictions may take some time to take effect. A study in France found that even after paraquat was withdrawn from the European Union market in 2007, paraquat continued to contribute to severe poisonings in mainland France and French overseas territories (Kervegant, Merigot et al, 2013). The study tracked a nine year period of poisoning cases reported to the Poison Control Centre in Marseille, starting and ending 4.5 years before and after paraquat was banned in the EU. While the most severe exposures resulted from deliberate ingestion, unintentional exposure continued. The total number of paraquat poisonings declined slightly after the ban (38 before vs 33 after ban), mainly as there were less unintentional exposures (21 vs 16). Most poisonings in mainland France were unintentional (accidental or occupational), while poisonings in overseas France were mostly due to self harm or accidents. Another study by Gutscher et al (2010) in nine European countries found most paraquat poisoinings between 2006 and 2008 were unintentional (27.0 % occupational and 27.7 % accidental), and these included fatal or severe cases.

A recent study in India highlighted dangerous application practices and related severe health effects for farmers. The authors are urging the Indian government to take regulatory action and ban paraquat (Kumar & Lakshmikutty 2015).

1.2 – ACUTE POISONING AND FATALITIES – OCCUPATIONAL OR ACCIDENTAL EXPOSURE

Paraquat is *very highly toxic to humans:* one small accidental sip is often fatal and there is no antidote. Several deaths from accidental ingestion of paraquat have occurred in the USA in recent years, often as a result of the concentrate being transferred into a beverage container. This is a major concern to US EPA. Like all pesticides paraquat (a 'Restricted Use Pesticide' in USA) must never be placed in a beverage container (Evans et al 2008).[8] In the case of paraquat, one sip is enough to kill a person *even if it is immediately spat out* (Buzik et al 1997). Possible symptoms of acute paraquat poisoning which may result from either oral or dermal exposure include the following: mucous membrane and airway irritation, abdominal pain, diarrhoea, vomiting, gastrointestinal bleeding, pulmonary oedema, dermatitis, renal and hepatic damage, coma, and seizures (Thundiyil et al 2009).[9]

The following studies (listed by region) indicate the continued problem of paraquat poisoning. Studies that address poisoning as a result of occupational or accidental exposure, as well as self-harm, are presented in this section. Studies exclusively focusing on self-harm are discussed in section 5.

1.2.1 – AFRICA

BURKINA FASO

UNEP, FAO 2010 – Paraquat most frequently identified pesticide causing poisonings in Burkina Faso[10]

"Pesticide formulations containing paraquat (Gramoxone, Calloxone, Gramoquat super, Benaxone) have alone caused 59 incidents, accounting for 20 % of the incidents [...] With regard to incident frequency rate, GRAMOXONE alone (paraquat 200 g/l) has been implicated in 54 intoxication cases and is the product which has caused the most health problems among agricultural producers. Three other pesticide formulations containing paraquat, i.e. CALLOXONE SUPER (paraquat 200 g/l), GRAMOQUAT SUPER (paraquat chloride 200 g/l) and BENAXONE (paraquat chloride 200 g/l) have been reported to be implicated in 5 intoxication cases, bringing to 59 the total number of paraquat-related incidents. Caustic lesions which characterized the initial phase of paraquat intoxication were found to be symptoms affecting some of the patients. (Mégarbane, 2003)" [p. ix, p. 36]

"Data collected to assess the adverse effects of pesticides on farmers highlights the recurrence of health problems related to the use of agro-chemicals. Out of 42 surveyed health centres, 922 pesticide-related poisoning cases have been recorded since 2002. In 22 of those cases, the incriminated pesticide formulations and the incident circumstances were identified. Five of the 22 cases occurred during pesticide applications in the fields. 296 intoxication cases which occurred during pesticide treatments were reported among agricultural producers. Paraquat, which has been implicated in 59 poisoning incidents has been identified as the most hazardous active ingredient found in pesticide formulations. [...] In view of their severe adverse effects on farmers, and in order to protect human health and the environment, special attention should be brought to active ingredients such as paraquat or endosulfan to effectively ban them and propose them for inclusion in Annex III of the Rotterdam Convention." [p. 49]

The study found that less than 1 % of farmers use the personal protective equipment recommended.

One author of the pilot study in 2010 in Burkina Faso emphasized the extremely high danger of paraquat:[11]

"Sylvain Ilboudo, a researcher at the Institute for Pharmacology and Toxicology at the University of Ougadougou, participated in a study on paraquat and said the chemical makes its way illegally into the country from neighboring nations such as

Ivory Coast, Ghana and Nigeria. The study found that numerous farmers in Burkina Faso have been poisoned by using paraquat. Investigators studied 650 farmers in three different regions in the country, finding that nearly half of them had suffered deleterious health effects due to chemicals used in agriculture, and 59 cases were very likely directly traceable to paraquat. Two people are thought to have died because of it.

«The study found that paraquat caused more problems than other herbicides,» Ilboudo said."

GHANA

WHO Regional Office for Africa 2014 – Paraquat identified as key cause of pesticide poisoning in Ghana[12]

"...pesticide-related poisoning events continue to occur countrywide in Kenya, with a total of 1 479 cases and 579 fatalities reported in 2012. In Uganda, pesticide poisoning incidents that occurred in 2012 in Wakiso and in 2013 in Pallisa caused a total of 87 fatalities. In Nigeria, pesticide poisoning in Kaduna State in 2012 resulted in an unconfirmed number hospitalized. [...] Ghana, for example, reported that application of various hazardous pesticides such as paraquat (WHO class II) and aluminum phosphide (a toxic fumigant) by farm workers without adequate protective clothing was a key cause of pesticide poisoning in the country." [pp. 31-5]

NPAS 2012 – Use of paraquat and other pesticides a major risk to farmers and public health in Ghana[13]

"There are six key aspects of the unsafe use of pesticides by farmers:

- Around seven banned or restricted chemical pesticides [...] appear to be still being used by some Ghanaian farmers. [...]
- Other dangerous chemical pesticides that the government has cleared for use and failed to ban are also being used, such as atrazine, *paraquat* and chlorpyrifos.
- Farmers are misusing pesticides by spraying too close to harvest (thus contaminating the crop before consuming it), over-applying the dosage, applying pesticides intended for cash crops to growing food crops or applying pesticides intended for growing crops onto stored crops, using obsolete or expired pesticides and mixing different chemical pesticides together.
- Most farmers fail to use any protective equipment while virtually no farmers use all the recommended equipment. *Only farmers contracted to cotton and cocoa companies receive protective equipment,* otherwise these need to be paid for. The health hazards are amplified given that some farmers allow their children to do the spraying.
- Storing pesticide containers near to, or even in, food stores is widespread and has contributed to *several recent deaths and an untold number of illnesses.* There is also widespread re-use of containers for storing food or water for humans or livestock.
- Many problems result from *insufficient training, advice and education provided to farmers* by the Ministry of Food and Agriculture (MOFA) and its extension service. Training is especially critical given that most farmers are unable to read and write. Less than half of all Ghanaian farmers have received such training; an NPAS survey in Upper East region found that 43 per cent of farmers sampled had had some training on the safe use of pesticides, but only just over half has received such training from MOFA; most of the rest had been trained by local NGOs. [...]"

NIGERIA

Gushit, Ekanem et al 2013 – Paraquat poisonings among farmers and pesticide retailers in Nigeria[14]

This study surveyed the practices and risks associated with use of herbicides by farmers, chemical retailers, and agricultural extension workers in Plateau State of Nigeria in 2010. Over half (ca. 56 %) of the farmers who use herbicides are unschooled and illiterate. Many farmers and retailers believed that herbicides are only slightly toxic, while all extension workers considered these to be highly toxic. Of 158 farmers 70 farmers (25.90 %) who were exposed to herbicides experienced one or more respiratory effect: irritation, coughing, choking or tight chest. Farmers suffered also neurological (16.65 %) and/or dermatological effects (25 %). Retailers reported having experienced similar respiratory effects and haematological symptoms (tiredness and weakness/anaemia) from exposure in the shop. Extensionists who were exposed to herbicides or other pesticides reported neurological effects (headache, dizziness, confusion, depression, coma, convulsions) or dermatological effects more often than respiratory effects. In the study area herbicides are now widely used.

The authors concluded that the low literacy rate and lack of knowledge about proper herbicide use resulted in an *indiscriminate use of herbicides* and that their use, if not properly addressed, presents a *threat to public health*. In a survey of 158 farmers, 52 retailers, and 40 extension workers the following points were observed:

- "Some health risk practices such as spraying the herbicides without safety kits like gloves, nose mask, safe boot, etc, are a common practice.
- *Many users of the herbicides complain of experiencing haematological, respiratory, neurological and dermatological related symptoms after using the herbicides.* Few farmers and the chemical marketers claim that they do not have any side effect.
- *There are reported cases of people and animals dying on exposure to herbicides like paraquat and 2,4-D within the study area.*
- Men and youths are observed to be at higher risk of exposure because they handle the herbicides most of the time.
- *Herbicides solutions splashing on the body of sprayers resulting in surface wounds was widely observed by the farmers.*
- Six herbicides were frequently used for control of weed by farmers within the state. These include: atrazine, 2,4-D-Amine, *paraquat,* glyphosate, pendimenthalin and propanil."

1.2.2 – ASIA

CHINA

Duan & Wang 2016 – Increase in paraquat poisonings in China; younger children accidentally poisoned[15]

"The *incidence of paraquat (PQ) poisoning in China is increasing* [...] accidental exposure to PQ occurred mainly in younger children (< 10 years)."

Among 71 poisoned children under 10 years 64 children (90.14 %) were accidentally exposed to paraquat and one case was fatal. Of 75 children over 10 years 46 children (61.33 %) ingested paraquat to self harm and 20 of these cases died. The mortality rate among these 146 cases of paraquat poisoning was 14.38 %.

Ge, Wang, and Sun 2013 – 22 children hospitalized with paraquat poisoning in Shandong province[16]

Over five years the Qilu hospital, Shandong University, treated 22 children who had ingested paraquat. In two cases children were poisoned by licking empty bottles of paraquat. One infant was poisoned by the mother who had ingested paraquat and afterwards fed him food after chewing it. Nine of the children died during hospitalization, five abandoned medical treatment, and eight improved and were later discharged. Mortality rate was 63.6 %. At least seven of the children developed pulmonary fibrosis. The authors of this study found that pulmonary fibrosis could not be reversed and that the prognosis of paraquat poisoning is still pessimistic even when a large dose of methylprednisolone was administered and prednisone was given over a long term.

Yin, Guo et al 2013 – Analysis of paraquat intoxication epidemic (2002–2011) in China[17]

A study in China concluded that there is an 'epidemic' of paraquat poisoning in the country. The national poison control centre recorded 1571 cases of paraquat intoxication consultation, of which 27.88 % (the largest ratio) occurred in 2010 and 23.62 % in 2011. From 2002–2010, there was an annual average increasing rate of 47.35 %. The most significant increase occurred in 2010, with an increase by 247.62 % over 2009 and 194.44 % in 2011 as compared with 2009. Poisoning occurred at all age levels. In 2010 the ratio of male to female was 46.47/49.14, of which 79.89 % were aged 18-64, and 14.06 % were under 18. The youngest reported case that year was aged 10 in the self-taking category, where 13.74 % were under 18 and 83.84 % were above 18; among the accidental ingestion cases, 52 (43.33 %) were under 18 and 61 (50.83 %) were above 18 years old. Self-harm accounted for most cases, 73.65 % of the total, with 13.56 % being a result of occupational exposure, and 12.48 % accidental ingestion or accidental expose. Occupational intoxications were mainly caused by skin and mucosa contact or respiratory tract inhalation.

Paraquat production and use has increased rapidly in China and the product is widely available. The study found that public understanding of the hazards of the chemical is insufficient. Many people misunderstood paraquat as a less-toxic herbicide. Paraquat management is poor: problems exist in the process of use and storage, the lack of safe keeping store counters, casual disposal of packaging after use or improper cap applications for liquids resulting in loose fittings and infant/child accidental contact. As a domestic industry, there remains insufficient worker protection within the production process, resulting in greater frequency of occupational poisoning that could lead to poisoning and even death. Many rural medical staff thought that paraquat is a less-toxic drug just as other herbicides and administered only gastric lavage or fluid infusion; extraordinary treatment protocols were often beyond their individual knowledge background.

Yu, Ding et al 2015 – Paraquat poisonings have highest fatality rate in Jiangsu, China[18]

Pesticide poisoning mainly occurred from July to September. The case-fatality rate of occupational poisoning (0.47 %) was lower than that of non-occupational poisoning (7.10 %). All 13 cities in Jiangsu Province reported cases of pesticide poisoning. Paraquat had the highest fatality rate (10.06 %) among all pesticides. In China pesticide poisoning cannot be ignored. Management and control should be improved in the production and usage of highly toxic pesticides including organophosphorus insecticides, rodenticides, and herbicides. The authors concluded that more attention should be paid to the protection of vulnerable groups including women, children, and the elderly.

FAO Regional Workshop 2014 – Liquid paraquat products banned in China, replaced by solid formulation[19]

Reports on local incidence relating to pesticides are very important. In China the decision to restrict or phase out certain pesticides was based on documented accidents (e.g. banning of fipronil as it killed bees and fish), regular exceedance of MRL [maximum residue limit] (leading to cancelling of registration for certain crops), or when records showed consistent misuse as a suicide tool. This led to cancellation of paraquat formulated as liquid concentrate. There have been numerous pesticide-related incidents and these were publicized in the media, causing great public concern. In principle, the China Crop Protection Industry Association supported the strategy to limit the '3 highs" – pesticides which exhibit high toxicity, high pollution or high residues. But the ban caused strong reactions of the industry and compromises for regulatory action were negotiated. A Chinese agrochemical company has developed a *solid* formulation of paraquat and it appears that this can still be marketed in China. Herbicides make up over half of the production in China; these are also exported.

Each year the Department of Agriculture seizes products that do not conform to information on the label, e.g. paraquat exceeding the allowable concentration of 13 %. [pp. 8, 9, 11, 14]

Zhang, Fang et al 2013 – High incidence of pesticide poisonings during farming season in Zhejiang, China[20]

Pesticide poisoning data were obtained from the Occupational Disease Surveillance and Reporting Systems (ODSRS) in Zhejiang province. The system includes data from hospitals and community healthcare centers in cities and clinics or medical dispensaries in rural areas. Annual pesticide poisoning cases and deaths in Zhejiang province remained constant from 2006 to 2010. All cases during this period were combined as study population, in total 20'097 pesticide poisoning incidents with 1413 deaths. There were 4'048 pesticide poisoning cases due to occupational exposure with 27 deaths and 16'049 cases due to non-occupational exposure with 1386 deaths. The death rate of non-occupational exposure (8.63 %) was higher than that of occupational exposure (6.67 %).

Among non-occupational pesticide exposure, there were 2448 unintentional poisoning cases with 56 deaths and 13'765

intentional poisoning cases with 1330 deaths, mostly due to pesticide-related poisoning and suicide (intentional fatal poisoning). Organophosphates caused the majority of all poisonings, with 13'391 cases and 1134 deaths (mortality: 8.47 %). Paraquat caused 461 poisoning incidents including 50 deaths; mortality: 10.8 %.

Pesticide poisoning was common in August and September, the farming season; poisonings during this period accounted for over 60 % of all occupational pesticide poisonings. Previous studies found that pesticide poisoning varied according to agricultural activities and high incidence correlated with pesticide availability in the farming season (Eddleston et al 2006; Mohamed et al 2009). In Zhejiang province more pesticide poisonings including fatal cases occurred during the farming season. There were more occupationally poisoned men in this season, presumably due to high occupational pesticide exposure. In China, estimates of the number of fatal poisonings suggest that over 150'000 deaths occur each year from pesticide poisoning (Li et al 2009). In Zhejiang province self harm and intentional ingestion accounted for 68.49 % (13'765/20'097) of all pesticide poisoning cases, while fatal intentional poisoning accounted for 94.13 % (1330/1413) of pesticide-related poisoning deaths. Suicide and self harm by ingesting a pesticide is a serious problem in the region, and the number of pesticide-related suicidal deaths increased with age. China has much higher suicide rates among the elderly than among young to middle-aged adults, and this pattern differs from other countries such as India (Phillips et al 2012). Ill health, increasing comorbidities, higher susceptibility to poisoning may contribute to a poor prognosis in China's older population.

The reporting system for pesticide poisoning (ODSRS) improves the rate of reported cases. But under-reporting still occurs in the new system for several reasons: (1) The system is largely based on hospital data. Provincial and municipal hospitals, most county hospitals and community healthcare centers, and a small percentage of rural clinics were included, but the overwhelming part of rural clinics were not. However, pesticide poisoning was much more common in rural areas. (2) Affected persons not seeking professional care, or consulting medical care outside the system, and misdiagnosis. (3) Poisonings from occupational exposure are often under-reported if the victims do not attend hospitals (London & Baillie 2001). (4) Fatal pesticide poisonings which occurred out of hospitals may not be reported to health authorities. (5) Patients with more severe pesticide poisoning – such as paraquat poisoning – will be transferred from community healthcare centers and rural clinics to provincial or municipal hospitals. These are often considered as 'survival', rather than being followed up, which may result in non-reported fatalities. Administrative resources may be lacking in rural areas (Zhang et al 2011). [pp. 2-3, 5-7]

See also: Zhou, Kan et al 2013 in Chapter 3.3.

INDIA

Pavan, M. 2013 – Acute kidney injury following paraquat poisoning in India[21]

Paraquat is a widely used contact herbicide in India. Paraquat poisoning is associated with high mortality varying from 35 % to 50 %. Six cases of paraquat poisoning were treated in a medical center in India. Acute kidney injury developed in all the cases and mortality was 66 %. Respiratory and multi-organ failures are the main causes for mortality. Five of the patients had ingested paraquat to self-harm, while one patient was exposed accidentally. Four of the patients died.

The authors concluded: "Paraquat consumption is a common agent of suicidal poisoning in this part of India, resulting in very high morbidity and mortality. There is no specific antidote for paraquat poisoning and the mainstay of treatment is supportive. Acute kidney injury is the common complication of paraquat poisoning and needs to be recognised and treated promptly."

IRAN

Davarpanah et al 2015 – Acute poisoning and severe lung fibrosis in farmer exposed to paraquat spray[22]

A 25-year-old male in reported good health was admitted to hospital in southern Iran due to nausea, vomiting, and severe substernal burning sensation after accidentally poisoning with about 100 mL paraquat concentrate (60 %). He was using a spray gun on a farm when paraquat solution was accidentally sprayed on his face and mouth and he instantly swallowed it, subsequently vomiting up the ingested solution. Gastric evacuation was followed by administration of activated charcoal and hemodialysis. CT scans of the chest revealed severe lung fibrosis three weeks later. The patient developed dysphagia and several oral ulcers. Endoscopy revealed multiple lesions in the throat and food pipe. Seven months later, the patient referred with shortness of breath; examination showed decreased breathing sound and the patient was admitted as an emergency case of pneumonia. Chest X-ray showed blisters in the lung causing the right lower lobe to collapse. The patient left hospital but developed dyspnea and fever three months later and was admitted again due to pneumonia. A CT chest scan displayed emphysematous lung and multiple large blisters in the right lung. The patient underwent thoracotomy, pneumolysis, bullectomy, and removal of part of one lung.

Goudarzi et al 2014 – Paraquat poisonings in Shiraz, Iran, due to accidental exposure and self harm[23]

At Shoushtari and Ali-Asghar hospitals in Shiraz, Iran, 52 patients were admitted due to poisoning with paraquat between 21st March 2012 and 20th March 2013. Of these 52 cases, 38 were attempted suicides and 14 were accidents. Twenty-seven patients died (mortality rate was 52 %); suicidal intention was one of the predictive factors of death. Paraquat poisoning is associated with high mortality requiring an immediate assessment of patients and prognosis.

JAPAN

Ito & Nakamura 2008 – Deaths from poisoning directly correlated to historical paraquat use (pre-2010)[24]

"We analyzed the number of deaths due to poisoning by pesticides over 38 years through vital statistics published annually by the Ministry of Health, Labour and Welfare of the Japanese

government, from 1968 through 2005. [...] Deaths from pesticide poisoning increased rapidly beginning in 1982, reached a peak in 1986 (death rate per 100,000 population: 2.6 in males and 1.7 in females) and declined gradually thereafter. In the most recent several years, these figures have declined to levels previously unseen (death rate per 100,000 population: 0.4 in males and 0.3 in females). [...] Deaths from pesticide poisoning were extremely well correlated to the history of paraquat. Through the 1985 Advisory Resolution on Paraquat Regulations by the Japanese Association of Rural Medicine and other public health-oriented efforts, the concentration of highly fatal paraquat formulations was reduced, leading to discontinuation of its production, customer identification was strictly enforced when purchasing pesticides, and people's safety consciousness regarding pesticides improved. We regard these developments as having had the greatest contribution to the reduction in deaths from pesticide poisoning. [...] Deaths from pesticide poisoning, observed quite frequently in the three prefectures of northern Kanto and Kagoshima Prefecture in 1986, continue to evidence a regional clustering properly termed 'rural poisoning'." [pp. 5, 9]

MALAYSIA

Sazaroni, Awang et al 2012 – Marked increase in paraquat poisonings in Malaysia after lifting of ban[25]

"A total of 278 calls involving paraquat were received during the period of the study [2005–2009]. The cases mainly involved adult males (68.4 %) and common among Indians (32.1 %) compared to Chinese (22 %) and Malay (22 %). Suicide attempts were the most common (73.8 %) circumstances of exposure. Accidental paraquat poisoning mostly involved exposure through ingestion (80.6 %), followed by inhalation (12.3 %) and cutaneous (7.1 %). The number of calls relating to paraquat exposure when it was banned was 67 (36 and 31 in 2005 and 2006 respectively). After its re-introduction, there was a marked increase in the number of cases: 39, 79 and 101 for 2007, 2008 and 2009, respectively.

Conclusion and Recommendations: There is an increment in the number of calls received by the NPC [National Poison Centre] involving patients exposed to paraquat from year 2007 to 2009 following the lifting of the ban. This should prompt the Government of Malaysia to review the lifting of the ban. Poor enforcement of regulations on paraquat use has resulted in intentional poisoning involving the chemical. Knowledge on the proper storage and disposal of paraquat must be imparted to its users. Similar study on a national level should be undertaken to have a more comprehensive data on paraquat poisoning."

Tan, JT et al 2013 – Increasing number of paraquat poisonings in Malaysia since ban was lifted[26]

"According to National Poison Centre, the number of paraquat poisoning cases has been rising in recent years. The sale of paraquat was banned from the year 2002 to 2006. Since 2006 when the ban was lifted, the number of paraquat poisoning cases reported has more than doubled up till the year 2008 where there was 7 times the number of cases reported compared to the years when it was banned (Sazaroni et al 2012). Paraquat poisoning remains a public health concern in Malaysia due to its high mortality and significant morbidity. However, there is limited publication of local data in regards to paraquat poisoning, particularly since the lifting of the ban in 2006. This study aims to describe the demographic characteristics, clinical features and outcomes of paraquat poisoning cases recorded in Hospital Taiping from 1st January 2008 to 30th October 2011. [...] The medical records of 79 patients were reviewed in this study. [...] The mortality rate in this study was 31.6 % (n=25). The outcome of 4 patients were not known as they requested discharge at own risk (AOR) and were lost to follow up. Majority of the patients reported intentional exposure (n=50, 69.6 %) with another 26.6 % were accidental (n=21). The rest of the cases were occupational exposure (n=3, 3.8 %). [...]

71 patients (89.9 %) had their urine paraquat result documented in their records. Of these patients, 38 (53.5 %) had positive results. [...] In a study conducted by National Poison Centre, suicide attempts were the most common circumstances of exposure with percentage as high as 73.8 % (Sazaroni et al 2012). This shows that over the last few decades, suicide remains the leading cause for paraquat poisoning and the lifting of its sales ban is not addressing the issue but facilitating it. Even though the majority of paraquat poisoning in Taiping are intentional exposures, we must not neglect the other 26.6 % of the cases which are accidental exposures. These exposures may be prevented if paraquat was not easily available as pesticides. Among the accidental exposures, unfortunately, 5 deaths were reported. [...]

In most cases, it is difficult to determine accurately the exact amount ingested. In this case, measurement of paraquat level in the plasma would be helpful. However, plasma measurement of paraquat is not routinely done in Taiping Hospital [...] in facilities without plasma paraquat measurement, urine paraquat testing may be the only option available to assess severity of exposure as well as prognosis. [...] We found that neither hemofiltration nor immunosuppressive therapies help to improve survival. It also has to be noted that both hemofiltration and immunosuppressive agents are costly treatments that can have significant financial impact, especially to resource-limited hospitals. With mortality rate of 54.2 % and 44.0 % despite hemofiltration and immunosuppression therapy respectively, paraquat remains a potent killer. The efficacy of these treatments is still debatable [...].

Recommendation: Paraquat poisoning is preventable through primary prevention by banning its usage in Malaysia. Relevant authority should look into alternative methods or less lethal compounds as herbicide. The burden of paraquat exposure, both intentional and accidental, is an unnecessary drain of our limited healthcare resources as the management of paraquat poisoning is at best supportive in nature as there is no known antidote. The high mortality associated with paraquat poisoning has also resulted in loss of productive group in our country. If the use of paraquat can be banned in other countries, the authors are of the opinion that similar measures can be taken in Malaysia." [p. 385, pp. 387-8]

PHILIPPINES

Quijano, R. 2012 – Health impacts from paraquat on banana and oil palm plantations in the Philippines[27]

The study investigated the impacts of pesticide exposure and the difficulties facing workers and communities affected by spray

drift. In the banana plantations, the investigative team took testimonies from three individuals. In relation to pesticides, testimonies claimed that workers often experienced adverse effects of the pesticides used in the plantation, including burning sensation and itchiness of the skin and face, difficulty of breathing, dizziness, abdominal pain, diarrhoea and other symptoms; especially those spraying the pesticides. Paraquat was widely used but the plantation recently switched to glyphosate products. The local medical doctor confirmed that the adverse effects from the pesticides used by the plantation were indeed being experienced by those who are exposed but was not sure about the effects of paraquat.

At a community assembly with oil palm workers, all complained of health effects from exposure to the chemicals used in the plantation, as well as low wages and working conditions. Most of the health complaints were burning sensation and damage to the skin and nails, especially on their hands and feet. Several complained of damage to their eyes, difficulty of breathing and chemical burns on their bodies due to pesticide spills from the backpack sprayer. The workers identified Gramoxone (paraquat) as the most common pesticide that caused the health problems. Other pesticides were not labelled. The symptoms identified were consistent with exposure to paraquat. A discussion with workers on a second oil palm plantation (Agumil Plantation Incorporated (API), in the town of Trento, Agusan del Sur) documented similar health complaints typical of paraquat toxicity. Respiratory symptoms such as asthmatic-like symptoms, coughing and easy fatigue were common. In addition to skin burns, some complained of deterioration of their vision and one was blind in one eye due to traumatic injury and exposure to paraquat. Follow up discussions with medical toxicologists from the National Poison Management and Control Center (NPMCC) at the Philippine General Hospital at the University of the Philippines Manila agreed that the signs and symptoms of pesticide poisoning were consistent with paraquat poisoning.

SOUTH KOREA

Cha, Jeong & Lee 2014 – Paraquat third-most used pesticide in South Korea 2007 to 2011 – now cancelled[28]

This study reviewed agricultural pesticide usage and trends and to identify hazardous pesticides for regulation, in terms of public health, in South Korea. The 50 pesticides with the greatest volume of usage accounted for 82.6 % of total use between 2007 and 2011, with the most-used active ingredient being machine oil, followed by mancozeb and paraquat (1'096 tons). Based on their toxicity and quantity of use, 24 of these pesticides were recommended for intensive regulation in South Korea. The authors concluded that intensive efforts are required for preventing potential health effects from these 24 pesticides selected for prioritization in South Korea. Registration of paraquat was canceled by the Korean government, while pesticide companies withdrew some other highly toxic pesticides (endosulfan and four organophosphates) in 2011. Several pesticides such as paraquat, pendimethalin, benomyl, and chlorpyrifos have also been reported in epidemiological studies to be related to cancer or neurologic diseases. In particular, paraquat was the most used herbicide in South Korea in both frequency and volume and has been a major causative agent leading to fatal poisonings (Lee et al 2013). Long-term health effects such as depressive symptoms (Kim et al 2013) and restrictive ventilatory defects (Cha et al 2012) have been reported among farmers who applied paraquat in South Korea. [pp. 283-4, 290-1]

Lee, Cha et al 2012 – Occupational pesticide poisoning among male farmers in 2010 in South Korea[29]

"The incidence rate of acute occupational pesticide poisoning was 24.7 (95 % CI 22.1–27.2) per 100 male farmers, which corresponds to [an estimated number of] 209'512 cases across South Korea in 2010. [...] The most frequently reported agents related with acute occupational pesticide poisoning were cartap hydrochloride (n = 105) followed by paraquat dichloride (n = 78) [causing 14 % of 555 reported poisonings] and fenobucarb (n = 69). The causative agents were mainly insecticides or herbicides. [...]

Acute occupational paraquat poisoning mostly occurred during paraquat application and produced symptoms of irritation. Agricultural work conditions including backpack application, low tendency to use personal protective equipment, and a hot and humid work environment may aggregate paraquat exposure and poisoning in South Korea. Therefore, to prevent both occupational and non-occupational paraquat poisoning, restricting its availability, including through an outright ban, is an important undertaking required in South Korea. [...] From a nationwide sampling survey of male farmers, we demonstrate that occupational pesticide poisoning is a major health problem in. Additionally considering chronic occupational pesticide poisoning cases, which were not included in this study, the actual magnitude of occupational pesticide poisoning could be much greater in South Korea. Despite the gravity of the problem, pesticide poisoning has received little attention in both research and policy. Therefore, more detailed studies investigating the risk of occupational pesticide poisoning and intensive intervention efforts to reduce pesticide poisoning are critical in South Korea." [p. 803, pp. 806-807]

1.2.3 – AUSTRALIA

Davey et al 2015 – Severe poisoning after accidental ingestion of paraquat[30]

A 17-year-old youth in Victoria accidentally ingested paraquat. He was initially managed at a regional hospital where continuous venovenous haemodiafiltration of blood was performed and anti-inflammatory medication was administered. He was later transferred to a transplant center for consideration of lung transplantation.

1.2.4 – EUROPE

Gutscher, Rato et al 2010 – Data on paraquat poisoning from poison centers in 9 European countries[31]

Aim of study: to collect data on adverse health incidents due to paraquat in Europe with a common standard.

Methods: Prospective multicenter cohort study based on data during 2006–2008 from poisons centers in nine European countries where paraquat was marketed, and retrospective pilot

TABLE 1 – **SEVERITY AND OUTCOME ACCORDING TO CIRCUMSTANCES OF EXPOSURE**

SEVERITY/CIRCUMSTANCES	OCCUPATIONAL	ACCIDENTAL	INTENTIONAL	UNKNOWN	TOTAL
asymptomatic	11	21	5	1	38
minor	55	45	20	2	122
moderate	11	11	13	2	37
severe	2	2	14	4	22
fatal	0	5	68	2	75
unknown	5	2	6	4	17
TOTAL	84 (27.0 %)	86 (27.7 %)	126 (40.5 %)	15 (4.8 %)	311

SOURCE: Gutscher K, et al. Multicentre data collection on paraquat poisoning in Europe. International Congress of the EAPCCT 2010, abstract 273; Clinical Toxicology 2010; 48(3): p. 303 (see also abstract 17, pp. 245-6). www.eapcct.org/index.php?page=congress1

study in the first months of 2006. Patient and exposure characteristics were recorded, and the likelihood of exposure, symptoms, severity, causality, and outcome were assessed. Only cases with a high likelihood of exposure are analyzed here.

Results: Total reported cases n = 419 (Greece 97, Spain 93, Portugal 84, United Kingdom 60, France 38, Italy 17, Belgium 6, Germany 12, Netherlands 8, Slovakia 3, Cyprus 1). Three hundred and eleven (74 %) had a high likelihood of exposure [to paraquat].

Patient characteristics: Adults n = 292, mean age 52.0 years (S.D. 18.2, range 16–92), children (age <16 years) n = 16, mean age 7.5 years (S.D. 4.5, range 1.0–15), unknown n = 3.

Among *occupational poisonings*, 2 were severe and 11 moderate, however outcome was unknown in 5 cases. *Accidental exposure* caused 5 deaths, 2 severe and 11 moderate poisonings; outcome of 2 cases was unknown. The route of exposure was oral in 161, dermal 62, inhalation 38, ocular 12, mucosal 2, combined 36. Paraquat could be analytically detected in 84 cases (52.5 % of all cases tested). Symptoms were mainly gastrointestinal, pulmonary, renal (via ingestion), and dermal. Paraquat poisoning is particularly prevalent in Southern Europe. Severe or fatal poisoning is more frequent in intentional than in accidental or occupational exposure.

FRANCE (MAINLAND AND OVERSEAS)

Kervegant, Merigot et al 2013 – Paraquat poisonings in Southern and overseas France continue after ban[32]

The study tracked a nine year period of poisoning cases reported to the Poison Control Centre in Marseille (PCC), starting and ending 4.5 years before and after paraquat was banned in the EU (in 2007). Unintentional poisoning continued during the whole period, while the most severe cases were due to deliberate ingestion. Between 2003 and 2011, the annual rate of pesticide-related suicide attempts or accidents reported to the PCC remained unchanged (approximately 65). A total of 71 cases of paraquat poisoning were recorded in the whole period (0.03 % of annual calls and 6 % of annual deaths), and 37 of these resulted from uninten-tional exposure. The data showed only a marginal decline in the total number of paraquat poisonings after the ban (38 before vs 33 after ban), mostly due to a lower number of unintentional exposures (21 vs 16). Fatalities decreased slightly from nine (before the ban) to six after ban, however there was no apparent change in the number of self harm cases attempted by using paraquat. In mainland France, most paraquat poisonings were unintentional (accidental or occupational), while in French overseas territories poisonings were mostly linked to self harm or accidental exposure. Exposure was located at the workplace in 16 cases (nine before and eight after the ban), garden in 7 cases (six before versus one after ban), and undetermined in 13 cases. The route of exposure was ingestion in 14 cases, dermal contact in 10 cases, and eye contact in 8 cases. Unintentional poisonings commonly occurred during preparation or application of spray solution. There was also one case of subcutaneous exposure while handling product in an experimental laboratory. Unintentional ingestions occurred during the opening of product container (e.g. twisting off bottle cap with teeth) or by blowing air through the spray nozzle to clear it. In mainland France after the ban, the number of paraquat poisonings decreased slightly due to a decrease in unintentional cases, especially during gardening (five cases before and one after the ban). In overseas French territories – where the proportion of self-harm cases was higher – paraquat poisonings did not appear to have decreased. The authors hypothesized that this may have been due to paraquat being more easily available in overseas French territories after the ban, via illegal import from neighboring countries (Suriname or Brazil). Despite the European ban and preventive measures, paraquat continues to cause severe, life-threatening poisonings in mainland and overseas France.

Nevertheless, this study shows that a ban is an effective measure to prevent unintentional poisonings.

GERMANY

Bertram, Haenel et al 2013 – Fatal poisoning after accidental ingestion of one mouthful of paraquat (20 %)[33]

"We report on a case of accidental paraquat poisoning in a 23 years old Caucasian man [in Germany], who developed respiratory fail-

ure due to pulmonary fibrosis. [...] Our patient was listed for high-urgency lung transplantation, because all of the described treatment strategies failed. We used extracorporeal support to bridge the time to transplantation, but the patient developed septic multiorgan failure and finally died [32 days after paraquat ingestion] before a suitable donor organ was available. In postmortem tissue specimen no paraquat could be detected, suggesting that lung transplantation would potentially have been successful."

IRELAND

Cassidy et al 2012 – Paraquat cases reported to Irish National Poisons Information Centre, 1999–2011[34]

"In July 2007, the Court of First Instance of the European Communities annulled the directive authorizing paraquat as an active plant protection substance. The aim of this study was to profile the epidemiology of paraquat poisoning by ingestion over a 13-year period and examine if the court ruling had an observable effect. Methods: A prospective observational study on cases reported to the National Poisons Information Centre (NPIC), involving the ingestion of paraquat-containing products was conducted from 1999 – 2011. [...]

Results: The NPIC was consulted on the management of 105 patients who ingested paraquat-containing products during the study period. Overall, there were 25 cases of accidental poisoning (11 adults, 14 children < 14 years). Fourteen (56 %) of these patients accidentally ingested a professional/concentrated product, 8 ingested a non-professional product, and the product formulation was unknown in 3 cases. 12/25 (48 %) patients were symptomatic, 12 were asymptomatic, and clinical features were unknown for one patient. There were 3 fatalities following accidental ingestion and all involved a professional product. Deliberate poisoning was reported for 80 cases (79 adults, 1 teenager aged 14 years). 37/80 (46.3 %) patients ingested a professional/concentrated product, 22 ingested a non-professional product and the product formulation was unknown in 21 cases. 68/80 (85 %) patients were symptomatic, 10 patients were asymptomatic, and clinical features were unknown for 2 patients. There were 34 fatalities (42.5 % mortality) following deliberate poisoning and a professional product was implicated in at least 24 of these fatal cases. Between 1999 and 2007, there were 96 poisoning cases reported to the NPIC. Following the European ban, 9 poisoning cases were reported between 2008 and 2011.

Conclusion: Deliberate ingestion of paraquat-containing products was associated with a 42.5 % mortality rate. A professional formulation product was known to have been ingested in 27/37 fatal cases. The number of cases of paraquat poisoning decreased dramatically after European ban was introduced in 2007."

English et al 2012 – Pesticide enquiries to the National Poisons Information Centre of Ireland, 2006–2010[35]

Results: 1030 cases of pesticides were reported over 4 years [May 2006 to April 2010]. [...] The majority of exposures occurred in a domestic setting (79 %), 6.3 % at work with others happening in open or unspecified areas. Enquiries related to herbicides (39.7 %), rodenticides (28 %), insecticides (17.5 %), molluscucides (6 %), unknown agents (3.2 %), mixtures of pesticides (1.9 %), fungicides (1.5 %), with moss killers and repellents both at 1.1 %. Eighty-one per cent of all cases were accidental; 7.4 % were deliberate and the remainder unknown. The route of exposure was mainly oral (55.5 %), followed by dermal (11 %), inhalation (10 %) and ocular exposures (4 %). In 13 % of cases multiple routes of exposure were reported. [...] Seven deaths (0.7 %) were reported during the study period. Five of these were deliberate paraquat overdoses."

1.2.5 – SOUTH AMERICA

ECUADOR

Meneses 2011 – Poisonings reported in Ecuador between 2008 and 2010 by Toxicology Information Centers[36]

Data from Ecuador national poison centers' report for 2008–2010

"Intoxication is a public health problem all over the world; Ecuador is not exempt from this world problem. Toxicology Information Centers (TICs) have been created to support intoxication matters. Experts made a review of statistics generated from TICs in Ecuador from 2008 to 2010, in order to know their contribution to knowledge about performance of intoxications. This review was based on some publications made by many TICs in the world, and on the guidelines set by World Health Organization (WHO) and International Chemical Security Program (ICSP)." Pesticide poisoning is a major public health problem in Ecuador, increasing at the rate of 15 % up to 35 % yearly.

Extract from Spanish text [translated by Stephanie Williamson, PAN UK]: 56 % of 1,961 poisoning cases were due to pesticides. Organophosphates, rodenticides and carbamates were the three most frequent groups of all chemicals, including pesticides reported as causing acute poisoning. Paraquat was eighth most common cause, with around 50 cases. The author noted that most of the reported pesticide poisonings were intentional [but did not give a breakdown by pesticide group] and highlighted that very toxic agents including trichlorfon (an OP), illegal rodenticide products, and paraquat accounted for more than one third of all poisonings reported to the TICs in Ecuador. Easy access via uncontrolled sales of household products is a major problem.

NICARAGUA

Corriols Molina 2009 – High incidence and underreporting of occupational pesticide poisoning in Nicaragua[37]

In 2000, in a representative cross-sectional survey of 3169 persons more than half (52.6 %) said that they had been exposed to pesticides and there were 72 cases of self-reported poisoning. Of this sample, 22 persons (or 30 %) stated that they sought either public health services or private care. In the same year the official register of Nicaragua recorded 1369 acute pesticide poisonings. Only one of the 22 cases that sought medical care was reported to the national register (less than 5 %). It was estimated that nearly 30,000 persons received medical care for pesticide poisoning, while these were not reported. Most cases were agricultural workers spraying pesticides in WHO Class Ia or Ib. Occupational cases represent only 38 % of the official records but 91 % of the cases reported in the survey, therefore occupa-

tional poisonings were clearly underreported in the poisoning register of Nicaragua. Intentional poisonings (suicides) and accidents were overrepresented in the register. Two of the most toxic pesticides, aluminum phosphide and paraquat, also accounted for a higher proportion in the official registry figures than in the surveyed sample (19 % and 10 % for paraquat, or 13 % and 4 % for aluminum phosphide, respectively). In the official figures of the acute pesticide poisonings registered in 2000, suicides accounted for 45 % and domestic accidents for 17 %, contrasting with 2.8 % and 6.8 % in the survey. Exposure to a pesticide in WHO Class Ia or Ib in the previous 24 hours to the occurrence of a poisoning was reported in 67 % of cases; 28 % of cases were caused by six Class II pesticides including paraquat and endosulfan, while Class III pesticides caused only 5 % of cases. The governments in Central America proposed to ban or restrict the 12 pesticides responsible for the greatest morbidity and mortality by acute poisoning in the region. [pp. 25, 27]

GUATEMALA

Campos 2002 – Most poisonings occupational; primarily caused by paraquat and four other pesticides[38]

In 2000, 60 % of the acute poisonings was due to occupational exposure, 27 % to accidental exposure and 13 % to suicide or suicide attempts. Lethality was 10 %. Each year the majority of the cases are caused primarily by 5 compounds: paraquat, methamidophos, methomyl, phosphine and endosulfan.

COSTA RICA

Espinoza et al 2003 – Paraquat among pesticides causing most poisonings in Costa Rica, 1996–2002[39]

Between 1996 and 2002, paraquat was the pesticide causing most acute poisonings, accounting for 34 % of the total. In 2001, the proportion of pesticide poisonings where the active ingredient could not be identified increased from 31.1 % to 37.7 %, while 40.5 % of cases were caused by four pesticides: paraquat, methomyl, glyphosate, and carbofuran. In 2002, 40.7 % of poisonings were caused by paraquat, methomyl, carbofuran, fenamiphos, glyphosate, 2,4-D, coumatetralyl, and diazinon. Paraquat was among 12 pesticides causing most poisonings in Central America.

EXPOSURE TO MULTIPLE PESTICIDES INCLUDING PARAQUAT

Prada P. 2015 – Employer must pay indemnity for worker's death likely to be caused by paraquat (Brazil)[40]

This newspaper article investigates a fatal case of occupational pesticide poisoning, the difficulty in proving a causal link to a specific pesticide, and the health problems of agricultural workers exposed to pesticides.

"Among the compounds widely sold in Brazil: paraquat, which was branded as "highly poisonous" by US regulators. Both Syngenta and Helm are licensed to sell it here. [...] A federal court upheld a ruling that forces Fresh Del Monte Produce Inc to indemnify the widow of a worker whose liver failed after repeated handling of pesticides. [...] Problems along the plateau emerged as early as 2008. [...] That July, Vanderlei Matos da Silva, a 31-year-old employee of Fresh Del Monte Produce, reported suffering headaches, fevers, a swollen belly and yellow eyes. For the previous three years, he had worked for the company stocking a pesticide ware-house at its pineapple plantation on the plateau. The job, according to documents and testimony by fellow workers submitted to a federal labor court, included mixing chemicals and preparing backpack dispensers for those who sprayed them. Silva also cleaned the warehouse and often stored unused chemicals in open containers, workers testified. The fumes often made him and colleagues dizzy. [...] One of the pesticides, according to worker testimony, was paraquat. A decades-old herbicide, paraquat is banned in the European Union and restricted for most uses in the United States. In Brazil, Syngenta, Helm and three other companies are licensed to sell it. The chemical is among those under review by Anvisa [national registration authority]. Paraquat is "highly poisonous," according to the US Centers for Disease Control and Prevention. Among other ills, according to the CDC, paraquat causes kidney, heart and liver failure. At least some of the paraquat sold to the Fresh Del Monte operation during Silva's employment there came from Syngenta, according to a 2007 sales receipt for 25,840 reais worth ($8,160) of the chemical. The receipt, obtained by prosecutors, was reviewed by Reuters. Syngenta declined to comment. By August, Silva could no longer work. In October, he was admitted to a clinic in Limoeiro and moved three weeks later to a bigger hospital in Fortaleza. He died a month later, leaving a one-year-old son and a widow, who began a years-long effort to win back pay and damages from Fresh Del Monte. The official cause of death was listed as liver and kidney failure and digestive hemorrhaging. Fresh Del Monte declined to comment on Silva's death. In court, the company's lawyers alleged that Silva had been diagnosed with a viral form of hepatitis unrelated to his work. The judge rejected that argument."

1.2.6 USA

AAPCC 2010-2015 – Increasing number of paraquat poisonings reported, mostly unintentional exposure[41]

In the USA, all 50 States, Puerto Rico and the District of Columbia each have regional poison control centers which record exposures to chemical substances, based on calls from the public or healthcare professionals. From 2010 to 2013, 57 poison centers submitted data on exposure to pharmaceutical products, consumer products, and toxic chemicals such as pesticides; 56 poison centers participated in 2014, and 55 in 2015. Unintentional and intentional exposures to toxic chemicals are a significant cause of illness and mortality in the US. Between 2010 and 2015, the majority of reported human exposures to paraquat were unintentional (see table 2).

In 2015, one fatal case was due to unintentional ingestion of paraquat, one fatality due to self harm, and one fatality resulted from malicious exposure (2015 annual report, pp. 961-2). In 2014, one fatal case was due to unintentional ingestion (2014 annual report, p. 1006). In 2013, two fatalities were due to unin-

tentional ingestion of paraquat from a beverage container, two fatalities were due to self harm, and one fatal case resulted from malicious exposure (2013 annual report, p. 1085). The circumstances of one fatal case in 2012 were not specified. In 2011, there was one fatality due to self harm (2011 annual report, p. 960). In 2010, one fatality occurred due to unintentional ingestion of paraquat and two fatalities were due to self harm (2010 annual report, p. 13). Of 14 fatal paraquat poisonings recorded during the past six years in the USA, five cases resulted via unintentional ingestion and two cases were due to malicious exposure (i.e. another person intended to harm the victim).

Calvert et al 2015 – Pesticides most often implicated in acute occupational illness / injury, 2007–2010 USA[42]

"During 2007–2010, of the 6,841 cases reported to SENSOR-Pesticides, 2,014 (29 %) were from occupational exposures and are included in the analyses. [...] counts and rates provided in this report must be considered minimum estimates. [...] Among persons exposed to herbicides, the specific herbicides most commonly involved were glyphosate and the dipyridyls (i.e., paraquat and diquat). A total of 81 % of cases were classified as low severity, 17 % were moderate severity, and 1 % were high severity. One affected person died." [pp. 7, 9]

Fortenberry et al 2016 – Paraquat and diquat cause majority (85 %) of all herbicide-related deaths in USA[43]

"A total of 300 paraquat- and 144 diquat-related acute illnesses were reported in 35 states and 1 US territory [...]. States in the western US accounted for the highest proportion of paraquat and diquat illness cases. Work-related paraquat and diquat exposures accounted for 68 % (n = 203) and 29 % (n = 42) of all paraquat and diquat cases, respectively. Among cases with paraquat-related illnesses, 83 % (n = 250) were exposed to paraquat only (the other 17 % were also exposed to other pesticides) [...]

Of the ingestion cases involving paraquat (n = 43) and diquat (n = 25), most were due to unintentional ingestion (58 % and 50 %, respectively) (Table 1, in Fortenberry et al 2016). Unintentional paraquat ingestion was commonly due to improper storage of the pesticide inbeverage containers (48 %; n = 12). Other less common unintentional ingestion cases included unintentionally ingesting while applying paraquat or diquat at work (n = 6; paraquat = 5, diquat = 1) swallowing paraquat while attempting to siphon it (n = 3), and not washing hands after diquat application and then using chewing tobacco (n = 1). In this study, intentional (i.e .suicidal) ingestion occurred in 5 % (n = 15) and 8 % (n = 12) of all paraquat and diquat-related illness cases, respectively. Ingestion (seven from unintentional ingestion and two from intentional ingestion) was responsible for 47 % (n = 9) of the 19 high severity, acute paraquat-related illnesses; and ingestion was responsible for 79 % (n = 19, seven from unintentional ingestion and 12 from intentional ingestion) of the 24 paraquat-related deaths.

Although most cases of acute paraquat-related illness were of low (41 %) or moderate (44 %) severity, death occurred in a total of 8 % (n = 24) illnesses, and all but one of these deaths were non-work-related. A total of 50 % of the deaths (n = 12), involved unintentional paraquat exposure: seven of these deaths involved unintentional paraquat ingestion from improper storage, including a 15-month old and 8-year old; two deaths involved exposure to paraquat from off-target drift; and, in three unintentional deaths, the exact mechanism of exposure could not be determined. [...]

Although paraquat accounts for only 6 % of all acute herbicide-related illnesses in the SENSOR-Pesticides data-base (n =

TABLE 2 – **AMERICAN ASSOCIATION OF POISON CONTROL CENTERS: PARAQUAT POISONINGS IN THE USA, 2010 TO 2015**

PARAQUAT EXPOSURE CASES			REASON				TREATED IN HCF*	OUTCOME				
Year	**Case mentions**	**Single exposure**	**Unintentional**	**Intentional**	**Other**	**Adverse reaction**		**None**	**Minor**	**Moderate**	**Major**	**Death**
2015	106	91	81 (76 %)	8	1	0	52	12	18	13	1	3
2014	90	69	65 (72 %)	3	0	0	38	13	13	7	1	1
2013	96	87	73 (76 %)	7	2	2	57	12	20	14	1	5
2012	86	73	65 (76 %)	5	5	1	44	11	16	8	2	1
2011	67	53	50 (75 %)	2	0	1	43	7	9	16	3	1
2010	76	63	56 (74 %)	6	1	0	46	13	17	9	2	3

SOURCE: AAPCC. Annual Reports of the American Association of Poison Control Centers' National Poison Data System (NPDS) for 2010, 2011, 2012, 2013, 2014 and 2015. www.aapcc.org/annual-reports

*Health care facility

This table was compiled by the author (R.I.) citing data from AAPCC's 28th to 33rd annual reports; see annual report for 2010 (p. 113), 2011 (p. 960, p. 1106), 2012 (p. 1165), 2013 (p. 1230), 2014 (p. 1093), and 2015 (p. 1067); the calculated percentage of *unintentional* exposures refers to data on single exposures.

Farmer showing paraquat bought in plastic carry bag. | © Dileep Kumar A. D.

2313), it accounts for 15 % of high severity cases of acute herbicide-related illnesses [...] Furthermore, the vast majority (85 %) of all herbicide-related deaths in the SENSOR-Pesticides and PISP databases were caused by either paraquat or diquat. Of the four herbicide-related deaths captured by SENSOR-Pesticides, paraquat and diquat were involved in 75 % and 25 %, respectively; in PISP, of the nine herbicide-related deaths, three were caused by paraquat, four involved diquat, one involved glyphosate, and one MSMA.

For cases with known application location, the vast majority of paraquat-related illnesses were related to agricultural applications while non-agricultural applications accounted for the vast majority of diquat-related illnesses (Table 2, in Fortenberry et al 2016). The majority of paraquat and diquat illness cases occurred in pesticide handlers (53 % and 54 %, respectively).

Health effects among the paraquat-related illness cases predominantly included dermal symptoms (42 %), such as skin pain, and rash (Table 3, in Fortenberry et al 2016). Ocular (34 %), neurological (27 %), and respiratory (24 %) symptoms were also observed. [...]

For paraquat-related illnesses, the most common root cause was failure to wear adequate personal protective equipment (33 %), especially eye protection (19 %) (Table 4, in Fortenberry et al 2016). Other common root causes were off-target pesticide drift from the application site (14 %), inadvertent spill/splash (not involving application equipment failure) (14 %), and application equipment failure (e.g., hose leaks and improper equipment assembly) (12 %). Many paraquat-related illnesses involving off-target drift were due to aerial applications that drifted from the application site to individuals who were engaged in their routine living activities (e.g. sitting or working in their yard) (41 %)."

EPA 2016 – Recommendation to prohibit all handheld application equipment for paraquat use in the USA[44]

The number and severity of human health incidents associated with paraquat in the USA is of great concern to the US EPA. Paraquat is highly toxic through all routes of exposure – ingestion, inhalation, and contact with the skin or eyes. Accidental exposure is common, resulting either from leaks, spills, or contamination during spraying, or from inappropriate storage in drink containers (contrary to label directions). The EPA concluded that additional mitigation measures are necessary to reduce paraquat's risks to workers and public health. In the USA paraquat is currently being re-evaluated. EPA has published a *Proposed Interim Mitigation Decision:*

"The EPA proposed to prohibit the use of all handheld application equipment, including backpack sprayers and hand gun sprayers, for paraquat dichloride. A large number of the paraquat incidents involve backpack leaks and accidentally spraying oneself while applying paraquat via handgun or backpack sprayers. Incident reports note that leakage and spraying of paraquat dichloride onto skin results in severe burns which can necessitate skin grafts, and sometimes death. The anticipated impact of this mitigation measure on human health risk associated with the use of paraquat is a decrease in dermal exposure and subsequently a decrease in occupational incidents."

The EPA also proposes restricting use of paraquat to certified applicators only, and requiring that all paraquat containers use closed system technology, and warning on label and training material for users to be updated.

EPA has finally decided that backpack and hand-held application methods will remain. However, to address the risks of accidental ingestion and occupational incidents, EPA will require that packaging for products designed for use with backpack and handheld application equipment must comply with the closed system requirements.

Waggoner, Henneberger et al 2013 – Pesticide use and fatal injury among farmers in the USA[45]

An analysis of 51,035 male farmers from North Carolina and Iowa farmers enrolled in the US Agricultural Health Study assessed whether pesticide use practices were associated with injury mortality. Researchers used Cox proportional hazards models adjusted for age and state to estimate fatal injury risk associated with self-reported use of 49 specific pesticides, personal protective equipment, specific types of farm machinery, and other farm factors collected 1-15 years preceding death. Cause-specific mortality was obtained through linkage to mortality registries. Researchers observed 338 injury fatalities over 727,543 person-years of follow-up (1993–2008). Fatal injuries increased with days/year of pesticide application, with the highest risk among those with 60+ days of pesticide application annually [hazard ratio (HR) = 1.87; 95 % confidence interval (CI) = 1.10, 3.18]. Herbicides were associated with fatal injury, even after adjusting for operating farm equipment, which was independently associated with fatal injury. Ever having used five of 18 herbicides (2,4,5-T, paraquat, alachlor, metribuzin, and butylate) was associated with elevated risk. The association between application of pesticides, particularly certain herbicides, and fatal injuries among farmers deserves further evaluation, with

particular focus on understanding timing of pesticide use and fatal injury.

Goldner, Sandler et al 2010 – Pesticide use and thyroid disease among wives of pesticide applicators in USA[46]
"Thyroid disease is common, and evidence of an association between organochlorine exposure and thyroid disease is increasing. From the Agricultural Health Study, researchers used North Carolina and Iowa data to assess the risk of thyroid disease in relation to ever use of certain pesticides. The data examined the etiology of thyroid disease among female spouses enrolled in the Study. Prevalence of self-reported clinically diagnosed thyroid disease was 12.5 %, and prevalence of hypothyroidism and hyperthyroidism was 6.9 % and 2.1 %, respectively. There was a significant association with hypothyroidism with ever use of the organochlorine chlordane (OR(adjusted) = 1.3 (95 % CI: 0.99, 1.7), the fungicides benomyl (OR(adj) = 3.1 (95 % CI: 1.9, 5.1) and maneb/mancozeb (OR(adj) = 2.2 (95 % CI: 1.5, 3.3), and the herbicide paraquat (OR(adj) = 1.8 (95 % CI: 1.1, 2.8)."

Lebov, Engel et al 2015 – Kidney disease risk among wives of pesticide applicators in the USA[47]
This study in the US investigated the relationships between end-stage renal disease (ESRD) among wives of licensed pesticide applicators (N=31,142) in the Agricultural Health Study (AHS). Paraquat was one of the target pesticides. The study examined the association between pesticide exposure and ESRD among farm wives. It considered (1) pesticide use, (2) exposure to the husband's pesticide use, and (3) other pesticide-associated farming and household activities. It found that: among all wives, overall use of pesticides was inversely associated with ESRD risk; among pesticide-applying wives, cumulative pesticide use was associated with ESRD; husband's use of paraquat and butylate was positively associated with ESRD in wives; ESRD rate increased with husband's increasing cumulative use of these pesticides. The study concluded that ESRD may be associated with direct and/or indirect exposure to pesticides among farm women. Future studies should evaluate indirect exposure risk among other rural populations.

1.3 – SKIN IRRITATION AND BURNS; SKIN ABSORPTION

Instituto Nacional de Salud Colombia 2011 – Occupational paraquat poisoning mainly via skin exposure[48]
Derivados bipiridílicos: Paraquat: "La intoxicación de origen laboral es poco frecuente, pero se puede presentar, siendo la principal vía de entrada la cutánea. El contacto frecuente produce lesiones tróficas y corrosivas en la piel y lesiones en uñas, las cuales se deforman y se caen." [p. 32]

Peiró, Zapater et al 2007 – Hepatotoxicity related to paraquat and diquat absorption through intact skin (Spain)[49]
A 69-year-old man, a farmer, was admitted because of continuous right-sided and central abdominal pain. He complained of coluria for the previous 2 weeks and the physical examination disclosed subconjuntival jaundice, conjunctivitis in the left eye, and hepatomegaly. [...] The patient was reinterrogated about a hypothetical exposure to toxic compounds and mentioned the professional use of herbicides without adequate skin protection. The herbicide contained a mixture of paraquat and diquat, and a case of hepatotoxicity to these compounds was suspected. Four weeks later, total bilirrubin had increased to 17.5 mg/dL without relevant changes in the rest of the analytical parameters except in the existence of a nonhemolytic, normochromic, and macrocytic anemia [...] Lipid peroxide levels were determined and showed a higher activity [...] Despite the empirical therapy, the blood tests continued to deteriorate. A second liver biopsy was done, and evidenced bile duct degeneration and ballooning degeneration of liver cells with marked cholestasis [...] The serum levels of total bilirubin gradually and spontaneously decreased, reaching normal values, and the patient was finally not considered for transplantation and was followed up at the outpatient clinic. Analytical controls were normal after 2 years. The patient was asymptomatic throughout this period. [...] We have classified our case as a probable bipyridyl-induced adverse reaction [...]. Both the high lipid peroxide levels observed in our patient and the development of macrocitic anemia are compatible with diquat/paraquat poisoning as previously reported.[16] Furthermore, the pathological findings are compatible with those observed in severe hepatotoxicity and, conversely, do not suggest alternative causes, such as alcohol, autonimmnunity, and virus.

Premaratna & Rathnasena 2008 – Skin burns from indirect contact with paraquat while handling a patient (Sri Lanka)[50]
"...the two patients described were accidentally exposed to paraquat in the vomitus of a patient who had ingested it, while attending to him. The vomitus had seeped through their clothing causing scrotal burns. The fact that they did not immediately remove the contaminated clothes would have aggravated the burns." [p. 103]

Soloukides et al 2007 – Fatal paraquat poisoning from minimal dermal exposure (Greece)[51]
"An 81-year-old male presented to his family doctor because of a skin lesion of the right thigh after accidental contact with paraquat the previous evening. His relatives reported that the pesticide was spread on the trousers, and the old man slept overnight without removing the clothes. The lesion was limited, producing only skin erosion, which was treated empirically with steroid ointments. Four days later, the patient complained of severe breathlessness and was admitted in our department [in Athens, Greece]. [...] His past medical history was unremarkable except for mild hypertension during the last four years which was treated [...]

Urine sodium dithionite test was negative for paraquat, and no pesticide was detected in blood sample. These findings indicated acute lung injury, acute renal injury, leucocytosis, and impaired hepatic function. The patient was treated with hydration, oxygen supplementation, and intravenous antibiotics. Renal failure was managed by hemodialysis and hemoperfusion. The lung function continued to deteriorate. He was transferred to the Intensive Care Unit, intubated, and ventilated, but died two days later. [...]

In conclusion, it is clear that even minimal dermal exposure to paraquat can be fatal, especially when associated with high

concentrations of the substance and/or significant delay in treatment initiation. The exact efficacy of the current medical management remains controversial. Therefore, it is crucial for emergency physicians to suspect paraquat poisoning when facing chemical burns and skin lesions and to investigate for the possibility of intoxication, particularly when skin lesions are associated with systemic symptoms." [pp. 375-376]

Tungsana, Chusilp et al 1983 – Acute poisoning after skin exposure to paraquat (Thailand)[52]

"Dermal exposure to paraquat, especially to the scrotum may produce serious systemic toxicity. [...] We present here a patient who developed a skin lesion and hepatic, renal and pulmonary injury following paraquat exposure to the perineum. The systemic toxicity was perhaps mild and unrecognized until 3 weeks later when blood chemistry was obtained. Although sepsis can mediate acute renal and respiratory failure, there was no fever or other clinical evidence of toxaemia. The failure to detect paraquat in blood and urine was not surprising so long after exposure. [...] In spite of the short exposure time, a concentrated preparation of paraquat was used, and the soft and highly vascular scrotal skin might allow significant absorption to produce systemic effects. This report adds to the literature on the potential hazards of exposure of normal skin to paraquat. Systemic effects are not common, but may occur especially when a concentrated solution contacts scrotal skin."

Zhou, Kan et al 2013 – Paraquat poisoning by skin absorption: Two case reports (China)[53]

"The present report describes two cases of paraquat poisoning by skin absorption. The cases involved contractual workers who were spraying paraquat in an orchard. Whilst spraying, some solution adhered to their skin. The skin developed erythema followed by blistering and hemorrhaging hemorrhagic diabrosis. Six days later the patients were admitted to the Department of Poisoning and Occupational Disease, Qilu Hospital of Shandong University (Jinan, China) with 3 and 2 % total body surface area (TBSA) burns, respectively. [...] paraquat may be absorbed through skin injuries, and since 1978 there have been several reported cases of severe paraquat poisoning by this pathway (Newhouse et al 1978; Bismuth et al 1982; Tungsanga 1983; Gear 2001). Since the beginning of its widespread use in 2000, acute paraquat poisoning has continued to be a major public health problem in the rural areas of China, normally from deliberate ingestion or accidental exposure (Ruan 2009). To the best of our knowledge, these instances are rare in China. [...] paraquat poisoning remains a severe health problem globally and the degree of the severity depends on the exposure route and dose. [...]

There has been a recent rise in case reports regarding paraquat poisoning following dermal exposure (Soloukides et al 2007; Peiró et al 2007; Lin et al 2003). In the two cases documented in this case report, the high temperature and humidity together with the lack of protection for the sprayers increased the risk of dermal exposure. In Case 1, the paraquat entered the body through the damaged skin and caused renal injury and pulmonary fibrosis. In Case 2, the paraquat caused serious skin injuries similar to that of Case 1. [...] These cases suggest that paraquat is well absorbed through abraded or injured skin and may result in severe toxicity."

1.4 – EYE INJURY AND IMPAIRED SIGHT

Adams et al 2013 – Eye injury from pesticides common in the UK; paraquat third-most frequent cause[54]

"6036 unintentional pesticide exposures were reported during the period [April 2004 to April 2012 in the UK]; 673 (11.1 %) of these cases involved eye contact. In 475 of these exposures eye contact was the only route of exposure. Five hundred and sixty-six (84.1 %) exposures involved adults; 103 children; 4 ages unknown. In 246 (36.6 %) exposures no symptoms were reported; 379 (56.3 %) reported eye irritation; 52 conjunctivitis; 45 eye burn; 34 abnormal vision; 35 lacrimation. The most common agent classes involved were: herbicides (265); insecticides (212); wood preservatives (83); sheep dip (37); fungicide (28); surface biocide (20); rodenticide (18); fumigant (4) and anti-fouling products (4). In 430 (63.9 %) exposures the pesticide was in use by the patient; 52 by another person; 59 exposures occurred after application; 64 due to unsatisfactory storage. One hundred and fifty-three exposures were occupational. Of the 566 adults: 62 (11 %) patients reported being exposed during windy conditions; 42 (7.4 %) reported hand-to-eye contamination; 13 reported using no eye protection. Five were exposed despite use of eye protection. [...] For exposures graded "moderate" the most common agents were: cresol/phenol (7); glyphosate (5); paraquat (5); tetramethrin (4); diquat (4); 2,4-D (4). [...] Eye contact with pesticides is a common route of pesticide exposure (11.1 %). Exposures frequently occur during patient use (63.9 %) and may result in moderate symptoms such as corneal burns (57, 12 %)."

Fernando & Perera 2011 – Severe eye injury from splash of paraquat (Malaysia)[55]

"We report a case of severe eye injury from paraquat to emphasize the need for proper and timely management. [...] The eye was washed immediately but she developed irritation, burning sensation and pain which became severe over the next few days. When she presented on the fourth day, she had ptosis and complained of poor vision, severe pain and difficulty in opening the eye. Her visual acuity was confined to hand movements. The conjunctiva was heavily oedematous and hyperaemic. Fluorescein staining revealed a large epithelial defect covering almost entire cornea. The anterior chamber showed a low-grade uveitis [...] A chemical injury therapeutic regime was commenced. [...] On the fifth day of treatment, she had no ptosis, no pain, the conjunctiva was minimally hyperaemic and the limbal ischaemia had reduced. On the 12th day the visual acuity of the eye was 6/6. There were no signs of eye injury. Timely and appropriate intervention can bring excellent recovery from paraquat eye injury as shown in this case."

Liu et al 2012 – Ocular burns caused by paraquat require hospitalization (China)[56]

"From June 2008 to Seprember 2010, 5 paraquat-induced eye burn patients were admitted in our hospital. The patients were treated with fist aid irrigation, eyedrops of heparin, antibiotics and own serum, ointment of rb-bFGF. Pseudomembrane of conjunctiva was separated. Amniotic membrane transplantation was given to a serious patient. [...] Paraquat-induced ocular burn patients have clinical characteristics of conjunctiva Pseu-

domembrane formation. Patients will recover well after a conventional therapy, Pseudomembrane separating and Amniotic membrane transplantation."

Uno 2015 – Eye injury with lesion of the cornea from exposure to paraquat (Japan)[57]

"An 82-year-old woman who had been exposed to herbicide containing paraquat in her left eye presented at Koumeikan Eye Clinic 2 days after the incident. Moderate corneal erosion was diagnosed and treated with ordinary medication, but the corneal lesion worsened. After administration of topical 2 % rebamipide eye drops, the corneal lesion resolved rapidly."

1.5 – EXACERBATION OF RESPIRATORY RELATED ILLNESS

Chatzi, Alegakis et al 2007 – Allergic rhinitis associated with paraquat use among grape farmers in Greece[58]

Main messages: Grape farmers who use pesticides in Crete have a high prevalence of allergic rhinitis and are occupationally exposed to a variety of pesticides. The highest risk was observed for use of bipyridyl herbicides (paraquat and diquat). A pattern of multiple pesticide use was found to be significantly associated with allergic rhinitis.

Policy implications: Although pesticides may contribute to respiratory symptoms and disease, there is insufficient evidence of their association with allergic respiratory disorders, and further studies are needed.

"In all, 78 (65 %) grape farmers reported that they used between 1 and 21 pesticides in their grape cultivations, with a median of 7 pesticides. The most often used herbicides were the broadspectrum, non-selective systemic herbicide glyphosate (n=67, 86 %), and the bipyridyl herbicide paraquat (n=38, 49 %). [...] Among herbicides, bipyridyls, including paraquat and diquat, had the highest OR for AR [allergic rhinitis] on the basis of symptoms reported in the questionnaire (OR, 2.2; 95 % CI, 1.0 to 4.8), and for the combination of AR with atopy [atopic syndrome] (OR, 4.0; 95 % CI, 1.4 to 11.2). [...] The highest ORs adjusted for other pesticides were found for bipyridyl herbicides (AR combined with atopy adjusted for glyphosate herbicide: OR, 3.5; 95 % CI, 1.0 to 11.9; adjusted for dithiocarbamate fungicides: OR, 2.7; 95 % CI, 0.8 to 9.8; adjusted for carbamate insecticides: OR, 3.7; 95 % CI, 1.1 to 12.9). [...] In the present study, bipyridyl herbicides were the group of pesticides most strongly associated with AR, both in single and multiple-agent models. This group contained the herbicides paraquat and diquat. Paraquat has been shown to cause fatal lung (mainly pulmonary fibrosis) and kidney damage in large oral doses, in animals and humans.[9, 17–19]"

Henneberger, Liang et al 2014 – Exacerbation of symptoms in agricultural pesticide applicators with asthma (USA)[59]

The study investigated whether exacerbation of symptoms is associated with farming exposures among agricultural pesticide applicators with asthma. Participants were pesticide applicators with active asthma (wheezing and breathing problems in past 12 months) who completed enrollment questionnaires for the US Agricultural Health Study (AHS). Exacerbation of asthma was defined as having visited a hospital emergency room or doctor for an episode of wheezing or whistling in the past 12 months. Exposures of interest were using 36 specific pesticides in the past 12 months and conducting various agricultural activities. The study suggests that use of specific pesticides, in particular paraquat and glyphosate, may contribute to exacerbation of asthma among individuals with allergies.

Hoppin, Umbach et al 2009 – Pesticide use and asthma among farmers in the Agricultural Health Study (USA)[60]

Although specific pesticides have been associated with wheeze in farmers, little is known about pesticides and asthma. Data from 19,704 male farmers in the Agricultural Health Study were used to evaluate lifetime use of 48 pesticides and prevalent adult-onset asthma, defined as doctor-diagnosed asthma after the age of 20 years. Asthma cases were categorised as allergic (n=127) and nonallergic (n=314) based on their history of eczema or hay fever. High pesticide exposure events were associated with a doubling of both allergic and nonallergic asthma. In pesticide users suffering from allergic asthma, symptoms were exacerbated when using a number of herbicides, including paraquat (as well as certain insecticides, one fungicide and two fumigants). There was little evidence that allergy alone was driving these associations. The findings are consistent with results from other respiratory analyses from the AHS and other studies: the herbicides EPTC and paraquat were associated with wheeze among farmers; paraquat was associated with allergic asthma among farm females, as well as respiratory symptoms and oxygen desaturation in studies of farmworkers in Costa Rica and South Africa; paraquat has been associated with allergic symptoms in grape farmers in Crete (Greece). The study concludes that pesticides may be an overlooked contributor to asthma risk among farmers. [pp.3-6]

1.6 – INADEQUATE DIAGNOSTICS AND ABSENCE OF TREATMENT

Agarwal, Srinivas et al 2006 – Treatment of paraquat poisoning remains mostly supportive; high mortality (India)[61]

Between 1998 and 2006 at Respiratory Intensive Care Unit in Chandigarh, India, 84 patients were admitted with a diagnosis of poisoning and acute respiratory failure. In five of these cases, paraquat poisoning was identified as the cause. All patients were initially treated at a primary health center. *Management of paraquat poisoning remains mostly supportive and treatment results were disappointing.* Currently there are no true pharmacological antagonists and no chelating agents capable of binding paraquat in blood or other tissue (Suntres 2002). Although immunosuppression was used in all of the severe intoxications, *only two of the five patients survived.*

Dias 2009 – Mass poisoning due to accidental ingestion of contaminated beverage in Sri Lanka[62]

"Five deaths occurred in a small hamlet close to Kandy [Sri Lanka] where it was suspected that an illicit brew, consumed by all

of the deceased when attending a village funeral, had poison mixed with it. Subsequent to these five deaths, 58 people from that village who became apprehensive sought admission to hospital. Twenty of them were asymptomatic. Some had abdominal pain, dyspnoea, faintishness and blurring of vision. Two of them died. Their post mortems showed the typical paraquat tongue and hemorrhagic changes in the lungs. There was sloughing of the oesophagus. The liver showed necrosis. The histopathological findings of the post-mortem specimen showed changes of paraquat poisoning. The sodium dithionate test confirmed the presence of paraquat both in urine and serum samples. Samples sent to the government analyst confirmed the poison as paraquat. [...] paraquat-based pesticides are widely used as a catalyst during brewing of kasippu. [...] During this unfortunate episode, the paraquat bottle had fallen into the container and contaminated the illicit brew. There had been no change in the taste or the odour, but a change in the colour had been noted. [...] Visitors who consumed the brew in large quantities had severe symptoms and died. Due to the chain of events which led a group of people to be acutely poisoned, it was possible to elicit the cause of poisoning. There may be unrecognised cases of chronic poisoning of paraquat due to accumulation of small amounts of paraquat in tissues. Due to unawareness, sporadic cases of acute poisoning may be missed even at postmortem." [pp. 69-70]

Eizadi-Mood et al 2011 – Supplementing conventional treatment of paraquat poisoning with antioxidant fails (Iran)[63]

A group of 29 patients treated between 2001 and 2005 at a hospital in Isfahan, Iran, was compared with 157 patients who had been treated for paraquat poisoning between 1985 and 2001. In the second study period antioxidants (vitamins C and E) were added to the conventional therapy but this did not reduce mortality rate. Paraquat poisoning was more common in men (76.6 %), young adults, i.e. age group 19 – 34 years (47 %), and during the summer (43.3 %). The failure of current treatments of paraquat poisoning calls for large prospective clinical trials on the treatment of paraquat poisoning and also for urgent preventive measures. [pp. 30-31]

Gil et al 2014 – More research needed on treatment modalities for attenuation of paraquat toxicity (South Korea)[64]

"Several methods have been studied for modifying the toxicity of PQ [paraquat] (8-12) over the past 40 yr, but none have proven to be effective to date. Therefore, the clinical outcome of PQ intoxication is usually determined by the degree of exposure (13, 14). Intentional ingestion of pesticide is a common way of committing suicide in Korea. Our pesticide intoxication institute therefore experiences a high incidence of acute PQ intoxication, with more than 10,000 cases during the past 30 yr. [...] it is difficult to determine which patients will survive in a clinical setting, because some patients with low PQ levels nevertheless die. [...]

In conclusion, treatment of PQ intoxication is not well codified. To date, most of the studies are prevalently performed in vitro or in animal models. However, based on our rich clinical experience, we believe a treatable group exists on PQ intoxication. Further studies are required to focus on improved treatment efficiency and on an expanded range of treatment groups." [pp. 1441, 1444, 1447-8]

Gosh et al 2012 – Difficult diagnosis and lacking tests for paraquat poisoning (India)[65]

"Despite widespread availability, reports of herbicide poisoning from India are not common. Diagnosis is often difficult in the absence of proper history, non-specific clinical features and lack of diagnostic tests. A case of Paraquat poisoning is reported where diagnosis could be established only after the recovery of the patient."

Kabade et al 2015 – Paraquat mortality high despite advanced medical care and prompt treatment (India)[66]

"In spite of advances in medical care, prompt treatment, and supportive care, mortality still remains high mainly due to multiorgan failure."

Khosya & Gothwal 2012 – Difficult diagnosis of paraquat poisoning at rural hospitals may enhance fatality (India)67

"Paraquat [...] is a broad spectrum liquid herbicide associated with both accidental and intentional ingestion, leading to severe and often fatal toxicity. Despite widespread availability, reports of herbicide poisoning from India are not common. Diagnosis is often difficult in the absence of proper history, nonspecific clinical features, and lack of diagnostic tests. We report two cases of fatal paraquat poisoning from a tertiary care hospital, Kota, Rajasthan, India. [...] The most frequent routes of exposure to paraquat, either accidentally or intentionally, in humans and animals are following ingestion or through direct skin contact. [...]. Direct contact with paraquat solutions or aerosol mists may cause skin burns and dermatitis. Paraquat splashed in the eyes can irritate, burn, and cause corneal damage and scarring of the eyes. [...] There is no specific antidote available for paraquat poisoning. It is important to establish the diagnosis early and to pursue aggressive decontamination and prevention of further absorption." [pp. 1-3]

Luo, Xian et al 2012 – No reduction of mortality via blood purification and immunosuppressive therapy (China)[68]

Blood purification and immunosuppressive therapy had no remarkable superiority in decreasing mortality of critically ill patients suffering from acute paraquat poisonning.

Marrs & Adjei 2003 – No successful therapies for paraquat poisoning[69]

"Intentional and accidental poisonings with paraquat have been a major cause of death in many countries. Most incidents are caused by ingestion of the concentrate intended for agricultural use. Local effects include damage to the skin, nails, mouth, eyes and nose. Sore throat, dysphagia and epigastric pain may occur. Systemic effects, which produce the fatal outcome seen in those who have ingested a sufficient quantity of paraquat, mainly involve the respiratory system. The changes in the lungs that underly the symptoms and clinical signs comprise a proliferative alveolitis similar to that seen in most experimental animals treated with paraquat. In most, but not all, patients who develop the characteristic lung changes, the condition progresses inevitably towards a fatal out-

come, death being due to respiratory failure. Numerous therapies have been tested, but none has been consistently successful."

Monteiro et al 2011 – Fatal paraquat poisoning in the absence of a positive urine test (Portugal)[70]

"Paraquat is a very toxic herbicide still available in Portugal [as of 2011] and a cause of many deadly cases. The diagnosis is emergent and sometimes complex. The prognosis is poor, mainly in cases of high doses intoxication as there is no proven effective therapy." The authors present a case of fatal paraquat poisoning with persistently false negative results in the urine test, highlight the low sensitivity of urine paraquat test in diagnosis and the importance of a blood test for prognosis; new effective therapeutic approaches are needed to change the fatal course of most of these poisoning cases.

Olson et al 2010 – Lacking diagnostics and medical facilities for treating poisoning in rural hospital (Honduras)[71]

A 20-year old man was admitted to a hospital in rural Honduras after he had ingested paraquat to self-harm. Paraquat levels in blood were not checked due to the inability to perform this test in a setting with limited resources. Despite standard supportive measures, the patient's clinical condition worsened and he died ten days later. A large number of paraquat poisonings from ingestion occur in developing countries without the possibility to measure paraquat blood concentration and arterial blood gases, or provide hemoperfusion and mechanical ventilation. [pp. 154, 156]

Peng et al 2012 – Hemoperfusion with continuous venovenous hemofiltration in poisoned patients (China)[72]

The combined therapy of hemoperfusion and continuous venovenous hemofiltration could prevent advances in lung injury induced by acute paraquat poisoning and prolong survival time, but failed to reduce mortality.

Saravu et al 2013 – Fatal case of paraquat poisoning in Karnataka, India; treatment options lacking[73]

"In this case, none of the strategies could work well. Most of the patients reported with paraquat intoxication are from agricultural background; usually such patients cannot afford the treatment expenses. This paper presents a fatal case of acute poisoning with paraquat who succumbed to acute respiratory distress syndrome (ARDS). [...] A 16-year-old female patient was admitted to emergency department of our tertiary care hospital with history of alleged consumption of paraquat poison, 13 days before [...] Since there is lack of clear evidence-based therapy for paraquat intoxication, different approaches have been tried for supportive management. [...] The data on paraquat poisoning from our country is scanty. [...] We did not find any significant benefits for the cyclophosphamide-dexamethasone regimen."

Sharma, Rai et al 2015 – Inadequate medical response to pesticide poisonings in India and rural Asia[74]

Pesticide poisoning kills hundreds of thousands of people in India each year. The majority are from deliberate self-poisoning with organophosphorus pesticides (OP), aluminium phosphide and paraquat. The current response from a public health, medical and research perspective is inadequate. There are few proven or effective treatments [...] Other classes of pesticide [besides OPs] that are common causes of significant and/or fatal poisoning [in rural Asia] include carbamate and organochlorine insecticides, the fumigant aluminium phosphide (a significant problem in north India), and the herbicide paraquat. [...] The case fatality for different pesticides also varies markedly, from around 70% for both aluminium phosphide and paraquat, to close to 0% for many of the newer lower toxicity pesticides (Dawson & Buckley 2007). [pp. 1-2]

Shi, Bai et al 2012 – Monitoring paraquat level in blood critical to clinical evaluation (China)[75]

"In conclusion, the plasma PQ [paraquat] concentration monitoring is critical for the clinical treatment of PQ intoxication. The examination of plasma PQ concentration was not only critical in the clinical evaluation but also helpful in guiding the treatment of such patients. As for patients with initial plasma PQ concentration below 200 ng/ml, the clearance effect of HP [hemoperfusion] was very limited and alternative therapeutic measurements with better effectiveness should be considered in priority so as to improve the clinical outcome. On the other hand, the dynamic monitoring of plasma PQ concentration can help physicians to identify rebound phenomena [paraquat in tissue reentering blood] and decide whether repeated HP treatments are necessary. So the examination of plasma PQ concentration should be carried out as a routine clinical laboratory test."

Simões et al 2012 – Paraquat poisoning: 18 years of experience at a hospital ward in Portugal[76]

"Paraquat intoxication has a poor prognosis with limited efficiency of treatment approaches."

Spangenberg et al 2012 – Paraquat poisoning: treatment options controversial (Germany)[77]

"As soon as further resorption has been prevented sufficiently, forced diuresis, renal replacement therapy, and hemoperfusion can be of help, but still remain controversial."

The amount of paraquat in a patient's blood is decisive for the outcome, rather than the total amount absorbed.

Su et al 2015 – Simple sensor for detecting paraquat (China):[78]

"disposable, stable, convenient, and easy to operate"

Chemical analysis of paraquat residues in urine is not straightforward. Developing this sensor further until it is ready for commercialization could provide an important tool for documenting workers' exposure to paraquat.

Zhou et al 2014 – Blood purification can prolong patient life but did not significantly improve survival rate (China)[79]

"Three blood purification methods can effectively remove paraquat absorbed into the blood, and the hemoperfusion combined with hemodialysis or continuous veno-venous hemofiltration can effectively reduce the degree of damage of liver and kidney and also can prolong survival time, but did not significantly improve the survival rate of patients."

2

Chronic health effects of paraquat

2.1 – SYNOPSIS

Parkinson's disease

Epidemiological studies have found an increased risk for *Parkinson's disease* in workers or residents who have previously been exposed to paraquat. This association has also been observed in tests on animals. Synergistic effects occur between paraquat and dithiocarbamate fungicides, in particular maneb and ziram (Wang et al 2011), and also between paraquat and iron (Peng et al 2007). As paraquat is eliminated from the brain much more slowly than from the liver, a single high dose of paraquat can have longer-lasting effects in the brain and interaction with other pesticides may also be possible later on after initial exposure (Moretto & Colosio 2011). Using MRI, microstructural changes were detected in the brain of agricultural workers who had a history of chronic exposure to low doses of different pesticides including paraquat (Du et al 2014). A meta-analysis of epidemiologic studies found that the risk for developing Parkinson's disease increased by about twofold in farm workers who had been exposed to paraquat, however to establish a direct causal relationship more studies are needed (Pezzoli & Cereda 2013). Farmers had a significantly higher risk of developing parkinsonism when they had not used protective gloves during pesticide spraying and if they previously used paraquat, permethrin, or rotenone (Furlong et al 2015). Elderly patients in Costa Rica who had been occupationally exposed to pesticides in the past performed worse in neurologic tests, and their risk of Parkinson's disease was increased (Steenland et al 2013). In the same area paraquat and maneb was used widely since 1970 on the main crop (coffee), indicating a possible causal link. In the USA, Tanner et al (2011) found an increased parkinsonism risk in farmers who were exposed to paraquat.

A meta-analysis of 46 epidemiological studies found a positive association of Parkinson's disease (PD) with herbicides and insecticides (van der Mark et al 2012). In another meta-analysis of 29 studies, occupational exposure to herbicides and insecticides increased the risk of PD significantly, while for a subgroup of six studies referring to paraquat there was a positive association of PD with paraquat that was significant after adjustment for confounders (Allen & Levy 2013). Registration of paraquat in the European Union was annulled on the basis that a possible link of paraquat with Parkinson's disease had not been properly considered and that several studies on potential exposure of workers had not been taken into account properly (COJ 2007).[80]

Exposure of human neuroblastoma cells (tumoric cells in endocrine glands) to paraquat and/or maneb led to increased levels of tyrosine hydroxylase and alpha-synuclein and lower activity of proteasomes that degrade damaged proteins in cells (Caputi et al 2015). The protein α-synuclein is known to be a key element in the development of Parkinson's disease when it aggregate to form fibrils (tiny fibres). Uversky et al (2002) found that paraquat increased the aggregation rate of α-synuclein significantly. Mathematical analysis of changes in enzyme activities indicated that paraquat perturbs processes linked to dopamine breakdown (Qi et al 2014). Paraquat led to a marked increase of α-synuclein in cell cultures of dopaminergic neurons (Chorfa et al 2013).

Yin et al (2011) found genetic background influenced paraquat neurotoxicity and that this may be related to iron levels in the brain (which paraquat can alter). In test on mice, paraquat and maneb were seen to impact on genes related to neural development, leading to reduced formation of new neurons (Desplats et al 2012).

In an epidemiological study in agricultural areas in California, genetic variability in the dopamine transporter protein (DAT) modified the impact of environmental exposure: in areas with high exposure to maneb and/or paraquat the risk for Parkinson's disease increased almost 3-fold in individuals who carried one allele with DAT susceptibility, and 4.5-fold in carriers of two or more susceptibility alleles (Ritz et al 2009). Residents living in areas with low exposure had no increased risk, even if they were carriers of one or more susceptibility alleles. The observation that genotype modifies the impact of pesticide exposure supports an association of exposure with Parkinson's disease (PD). In another study, Goldman et al (2012) found an 11-fold increase in risk for PD among farmers who had been exposed to paraquat and were carriers of a genetic deficiency for glutathione S-transferase (GST class T1), an enzyme which deactivates oxidation products that damage brain cells. As about 20 % of Caucasians have deficient GST T1 a large population is at risk of PD via potential exposure to paraquat.

An analysis of 12 epidemiological studies found overall increase of 28 % in risk for Parkinson's disease among workers who had been exposed to multiple pesticides (Van Maele Fabry et al 2012); the result was consistent for 'herbicides' when data was substratified by pesticide type. Mitochondrial activity was found to correlate with exposure to ambient pesticides known as mitochondrial inhibitors, both for individuals with and without a diagnosis for PD (Bronstein et al 2015). Hatcher et al (2008) emphasized that animal studies have shown that paraquat is able to cross the blood–brain barrier and can cause reproducible loss of dopamine neurons.

Impaired lung function

Paraquat was associated with long-term respiratory defects among fruit growers in South Africa (Dalvie et al 1999). Cumulative paraquat exposure caused abnormalities in gas exchange in the lung (Schenker et al 2004). Occupational exposure of gardeners, horticulturists, or farmers in the Netherlands to pesticides (herbicides and insecticides) was associated with clinically relevant progressive annual declines in the lung function. This effect was significantly larger in those who had ever been or were smokers, and even stronger in a subgroup of gardeners, horticulturists and nursery growers (de Jong et al 2014). After separating the subcategories 'insecticides' and 'herbicides' the strongest association was seen for a low exposure to herbicides. Within the region of the study, paraquat and diquat were the most commonly used herbicides on potatoes in the years after 1980, therefore it appears very plausible that paraquat was linked to the observed respiratory effects. Similar results were found with farmers in South Korea (Cha, Lee et al 2012).

Immunotoxicity and dermatitis

Paraquat has the potential to damage the immune system (Paolillo et al 2011). A single dose of paraquat in mice resulted in marked reduction of proliferative responses in T and B lymphocytes and significant reduction of IgM plaque-forming cell counts. B cell responses to antigens were also inhibited, indicating an immunotoxic effect at doses equivalent to the acceptable daily intake and below some MRLs for certain food or animal feed. Higher concentrations paraquat appear to deplete immune functions, while lower doses could alter immune responses toward a proinflammatory profile such as that of TH17 cells. These have been strongly implicated in autoimmune diseases, therefore regulatory measures for paraquat need to be revised (Hassuneh et al 2012). Okabe et al (2010) observed that paraquat reduced productivity of immunoglobulins in mouse lymphocytes and stated that possible risks to the immune system from paraquat residues in plant foods should be assessed. In natural killer cells from mice (cell cultures) exposure to paraquat led to reduced activity (Lim et al 2015). Mangano et al (2012) observed that interferon-γ, a proinflammatory cytokine (signaling protein), plays an important role in paraquat-induced neurotoxicity, along with tumor necrosis factor-α (Litteljohn et al 2011). Exposure of workers to paraquat can cause severe skin irritation and dermatitis (chronic skin inflammation).

Endocrine disruption and reproductive toxicity

Paraquat is listed as a 'potential endocrine disruptor' (TEDX 2016). In Malaysian farmers who were exposed to paraquat a significant decline in semen quality was observed (Hossain et al 2010). In animal tests paraquat affected embryonal development (Hausburg et al 2005), and reproductive or teratogenic effects have been observed (Lewis 2004). Epidemiological studies found an increased risk of birth defects in children of male workers who had been exposed to paraquat (Garcia et al 1998).

Genotoxicity

Epidemiological studies found an association between leukemia in children and exposure of their mothers to paraquat (Monge et al 2007). In other studies paraquat was associated with non-Hodgkin's lymphoma (Park et al 2009), brain cancer (Lee et al 2005), skin melanoma (Wesseling et al 1999 & 1996), and potentially cancer-promoting mutations in skin cells (Van Osch et al 2010). Skin cancer (squamous-cell carcinoma) was confirmed in a farmer in the UK who had been exposed to paraquat spray solution through a leaking backpack sprayer (Anderson & Scerri 2003). In the USA, the risk of breast cancer was slightly increased among women whose husbands had used paraquat (Engel et al 2005). Paraquat had mutagenic potential in several tests on rodent cells and was linked to an increased incidence of adenomas in the lung of rats; high doses caused chromosome damage in bone marrow (Marrs & Adjei 2003). In tests on rats chromosomal damage resulted after paraquat exposure via skin (D'Souza et al 2005). Vivarelli et al (2013) found that paraquat induced DNA damage and promoted changes in the splicing pattern of genes involved in DNA repair, cell cycle control, and apoptosis.

Kidney damage

An epidemic of chronic kidney disease has ocurred over the last decade in Central America in young male agricultural workers. The causes are not known but it has been surmised that pesticides could be one factor contributing to this, along with heat stress and dehydration (Correa-Rotter et al 2014). Based on previous use of pesticides (mostly herbicides) in plantations in Nicaragua evidence was strong for a potential association between paraquat and acute kidney damage, but limited for chronic kidney insufficiency (McClean et al 2010).

2.2 – PARKINSON'S DISEASE

A) CASE REPORTS

León-Verastegui 2012 – Parkinson's disease due to occupational paraquat exposure in Mexico[81]

"La historia clínica fue la piedra angular en el caso decrito. Con los elementos coadyuvantes como el análisis específico del puesto de trabajo y la literature médica revisada, se estableció que la exposición a paraquat generó la enfermedad de Parkinson. Por lo tanto, se trató de una enfermedad de trabajo."

"The aim of this paper is to describe a clinical case of occupational medicine in Parkinson's disease in occupationally exposed workers to paraquat, elevating the importance of medical history work, which was the key to the clinical case study."

The authors concluded that in this particular case previous exposure to paraquat had caused parkinsonism, and this was treated as an occupational disease.

B) ORIGINAL RESEARCH ARTICLES

Allen & Levy 2013 – Occupational exposure to herbicides (paraquat) increases risk of Parkinson's disease[82]

This meta-analysis pooled studies on a potential association between pesticides and Parkinson's disease (PD) and analyzed overall pesticide exposure arising from occupational pesticide use and non-occupational use. The summary effect size (ES) or odds ratio from the 28 case-control studies and one cohort study was 1.42 (95 % CI 1.32–1.52) in the fixed-effects model, a significantly positive association between PD and overall pesticide use. The summary ES by a random-effects model suggested an even greater association (1.63 with 95 % CI of 1.37–1.93). Study-specific ES were strongly heterogeneous. Only two studies that were included showed negative associations between PD and pesticide use (Nuti et al 2004; Ritz & Costello 2006). The summary ES for the association between PD and occupational pesticide exposure was 1.49 with 95 % CI of 1.34–1.66 (in a fixed-effects model); strength of association was comparable to that of overall pesticide exposure.

To account for confounders on the relationship between PD and pesticide exposure, crude ES (unadjusted for confounders by analysis models or in study designs) and adjusted ES were extracted separately from studies. Six case-control studies which specified particular pesticides referred to paraquat exposure. The summary ES for all chemical groups and pesticides suggested positive associations with PD, except for DDT and parathion. The summary ES for organochlorines (adjusted ES) and paraquat (adjusted ES) were statistically significant, while positive associations of PD with organochlorines and with paraquat based on the crude ES were not significant. The summary ES for PD were heterogeneous for exposure to paraquat and organophosphates (using the adjusted ES).

Both occupational herbicide and occupational insecticide exposure showed a significant association with PD. The summary ES for the development of PD suggested a statistically significant association with exposure to herbicides and insecticides, both overall and occupational exposures. However, there was a heterogeneity among the pooled studies ($p \leq 0.01$), with the exception of occupational herbicide exposure. In general, a positive relationship appeared stronger when analysis was limited to occupational exposure only. A stronger association with PD for occupational herbicide, compared to that of overall exposure, may reflect a tendency of risk increasing with exposure intensity, duration and/or frequency. The results of this meta-analysis suggest positive associations of herbicide and insecticide exposure with increased risk of PD. It may be speculated that causative agents in the pathogenesis of PD exist among insecticides and herbicides, such as paraquat.

Caputi, Caretta et al 2015 – Paraquat induces dysfunction of proteasomes in neuroblastoma cells[83]

The findings in this study contribute to confirm the biochemical alterations of tyrosine hydroxylase and alpha-synuclein induced by exposure of neuroblastoma cells (tumor cells in endocrine gland) to paraquat and maneb. These changes are probably related to dysfunction of proteasomes, protein complexes in the cell that degrade damaged or unneeded proteins. Tyrosine hydroxylase levels were significantly increased following exposure to paraquat alone and paraquat combined with maneb. Levels of alpha-synuclein were significantly increased in cells exposed to paraquat alone or in combination with maneb. (Abnormal aggregates of α-synuclein protein – termed 'Lewy bodies' – appear in brain cells of patients with Parkinson's disease.) A concurrent reduction of proteasome subunits and expression of the opioid receptor gene was also observed. The latter resulted in a significant down-regulation of the opioid receptor. These effects, caused by pesticides under particular test conditions, could help clarify the relevance of different biological markers involved in Parkinson's disease.

"Present data showed different alterations triggered by pesti-cides exposure of SH-SY5Y cells, supporting the hypothesis thatUPS and opioid receptor gene expression changes, induced bypesticides, may play a role in pathophysiological mechanism-sunderlying PD. Cell exposure to pesticides showed a dose-and time-dependentdecrease of cell viability even though PQ induced a more pro-nounced cell mortality compared to MB, supporting the hypothesisthat PQ may exerts a stronger neurotoxic effect.

In conclusion, the findings contribute to confirm the biochemical TH and α-syn alterations following different schedules of PQand MB cell exposure, probably related to proteasome dysfunction." [p. 900]

Czerniczyniec, Lanza et al 2015 – Function of striatal mitochondrial impaired by acute paraquat poisoning[84]

In tests on rats paraquat exposure reduced activity of cellular respiration enzymes complex I and IV by 37 % and 21 %, respectively, in mitochondria of neurons of the striatum. Paraquat induced dysfunction caused both by redox reactions and impairment of the mitochondrial electron transport chain, causing oxidative damage. As a consequence, dysfunction of mitochondria could probably lead to alterations in cellular bioenergetics.

Desplats, Patel et al 2012 – Exposure to paraquat/maneb impacts on genes regulating neuron formation[85]

Adult brain development/neurogenesis is highly susceptible to multiple risk factors for Parkinson's disease (PD) including accumulation of alpha-synuclein protein, specific genetic mutations and exposure to toxins, namely maneb and paraquat. (Alpha-synuclein is involved in neurotransmission at the ends of neurons.) Each of these factors, alone or combined, extensively affects expression of genes that regulate growth and fate of stem cells such as neuronal differentiation and duration of survival. This study on mice identified genes which respond to risk factors: genetic variability (of α-synuclein accumulation or specific mutations), exposure to toxins (such as maneb and paraquat), or a combination of genetic and environmental factors. A model

integrating well-known molecular pathways leading to PD was proposed in which maneb and paraquat interfere with the metabolism of mitochondria by producing reactive oxygen species that cause oxidative stress and contribute to inactivation of transcription factors and result in misfolding and aggregation of α-synuclein. When combined, these factors impact on genes related to neural development, leading to reduced adult neurogenesis (formation of neurons).

Dhillon et al 2008 – Risk of Parkinson's disease possibly 3-fold increased in workers exposed to paraquat[86]

In this case-control study, 100 patients with Parkinson's disease in Texas were questioned on their previous use of pesticides and past exposure. A possible association of an increased risk for Parkinson's disease was observed with personal use of paraquat (OR: 3.5; 95 % CI 0.4–31.6; p = 0.243). The number of subjects (four) reporting paraquat exposure was relatively small and the result was not statistically significant. [pp. 40, 45]

Du, Lewis et al 2014 – Microstructural changes in brain of farmers exposed to paraquat or other pesticides[87]

Recently, magnetic resonance imaging has been explored extensively to study pathological changes related to Parkinson's disease (PD) in humans. In particular, diffusion tensor imaging (DTI), by measuring microstructural disorganization due to loss of dopamine cells, has shown promise as a tool for detecting PD-related changes. In tests on mice DTI changes were associated with dopamine neuron loss in the substantia nigra (SN). Several human studies have demonstrated reduced fractional anisotropy (FA) values in the SN of early PD patients, indicating that DTI changes may be able to detect changes in the brain in vivo. Twelve male subjects, all with a history of applying various pesticides including paraquat for at least eight years, were compared with 12 PD patients and 12 healthy subjects (control group). There were significant differences in fractional anisotropy of the SN, and PD subjects had significantly lower FA in the SN. Compared to control subjects, pesticide-exposed subjects showed a significantly lower FA value in the SN, while three other parameters showed no significant differences. Compared to PD subjects, the pesticide exposed subjects showed no significant difference in FA, but were significantly lower on the other three measures.

This study is the first to demonstrate directly the microstructural changes in the brain (substantia nigra / SN) of humans who have had chronic, low-dose exposure to several different pesticides (mean number of pesticides: 10.8; standard deviation: 4.8). Local changes detected by MRI may represent one of the "hits" leading to parkinsonism. The results showed that DTI could be a potential in vivo marker for microstructural changes caused by environmental risk factors of PD. All of the exposed subjects in the study had been exposed to paraquat, and participants were matched for age. Due to the limited sample size and also as FA measurement is nonlinear it was not possible to assess if the changes in SN were primarily due to specific pesticides. These findings are consistent with the role of pesticide exposure initiating or accelerating pathological processes similar to those occurring in PD, as previous studies have indicated. [pp. 2-3, 5-6]

Furlong et al 2015 – Protective gloves and hygiene practices modify risk for Parkinson's disease partially[88]

This case-control study included over 52'000 pesticide applicators from the Agricultural Health Study in the USA. It investigated how the use of gloves and workplace hygiene modified associations between pesticides and Parkinson's disease (PD). Use of protective gloves and hygiene practices partly modified the associations of paraquat and permethrin with PD: neither pesticide was associated with PD among 'protective glove users' (≥50 % glove use), while both pesticides were associated with PD among 'glove non-users' (< 50 % glove use), with an odds ratio for paraquat of 3.9 (95 % CI 1.3, 11.7) (p < 0.05), while for permethrin OR was 4.3 (95 % CI 1.2, 15.6). Rotenone was associated with PD regardless of glove use (OR = 5.3; 95 % CI 1.3, 20.5), and trifluralin was associated with PD (OR = 1.7; 95 % CI 0.6, 4.7) only among those farmers who used less than two hygiene practices. All four pesticides were included in models adjusted for personal protective equipment (PPE) and hygiene (using a variable for PPE and a hygiene variable). The associations of PD with previous paraquat use (used once or more times before the reference date) were statistically significant (p < 0.05) in three models:

(a) OR: 2.5 (95 % CI 1.3, 4.8); adjusted for state, smoking, sex, and age
(b) OR: 2.4 (1.1, 5.1); as (a), additionally adjusted for 3-category glove variables, dichotomous hygiene variable
(c) OR: 2.6 (1.1, 6.1); as in (b), additionally adjusted for the other pesticides rotenone, permethrine, trifluraline

Associations of PD with rotenone were also significant (p < 0.01). Protective glove use and hygiene practices were important modifiers and these factors were associated with a reduced risk of PD among all users of all pesticides. Additionally, strength of association between several pesticides and PD varied according to PPE or hygiene. Modification of the PD–pesticide association by use of PPE and hygiene practices was assessed in five separate models; results of model 3 are reported above. Glove use and hygiene practices may reduce risk for PD. However, even among *farmers who used gloves in over 50 % of cases,* paraquat use was linked to a slightly elevated risk for PD (OR = 1.3; 95 % CI 0.5, 3.9), although this was not statistically significant. It is noteworthy that previous studies on the cohort of the Agricultural Health Study indicated that using protective gloves was the most important protective factor.

Gatto et al 2009 – Paraquat in drinking water or ambient air increases risk of Parkinson's disease[89]

"The PD relative risk associated with a combined exposure to pesticides in the environment and in presumably contaminated well water was greater than that associated with ambient exposure alone. These results suggest that, whereas exposure to the selected pesticides in the environment alone increases the relative risk of PD (20–50 %), exposures from consumption of potentially contaminated well water may confer some additional, independent risk above ambient exposure."[p. 1916]

"For the six pesticides we individually examined, for example, among subjects who were ambiently exposed to chlorpyrifos at

TABLE 3 – **RELATIVE RISK OF PD FROM POTENTIAL INHALATION AND INGESTION OF PESTICIDES: *PARAQUAT***

EXPOSURE (BASED ON LAND SURVEY, USE DATA)	CASES/ CONTROLS	ODDS RATIOA* (95 % CI)
Unexposed	131/140	1.0 (reference)
Ambient pesticide only	158/141	1.15 (0.82–1.62)
Ambient and well water	79/60	1.19 (0.77–1.83)

*a Adjusted for age, race, sex, education, and family history of PD.

SOURCE: Gatto NM, Cockburn M, Bronstein J, Manthripragada AD, Ritz B. Well-water consumption and Parkinson's disease in rural California. Environmental Health Perspectives 2009; 117(12): 1912-8. http://dx.doi.org/10.1289/ehp.0900852

their residences, 80 % were also exposed to diazinon and 91 % to paraquat; of subjects ambiently exposed to paraquat, 73 % were also exposed to diazinon, 82 % to methomyl, and 80 % to propargite. Thus, it was also impossible to estimate the effects for all of the six pesticides together in the same model, that is, to estimate the effect for one chemical while adjusting for all others. [...]

In conclusion, our study, the first of its kind to apply a semi-quantitative approach to estimating pesticide exposure in well water, contributes evidence that consumption of well water potentially contaminated with pesticides may play a role in the etiology of PD." [p. 1917]

Goldman et al 2012 – Individuals with deficient GST T1 at increased risk of parkinsonism from paraquat[90]

The enzyme glutathione S-transferase (GST) protects cells from oxidative stress and could potentially modify paraquat toxicity. Among participants of the Agricultural Health Study in the USA, a group of 87 farmers diagnosed with Parkinson's disease (PD) was compared to a control group who did not have PD. The genotype was determined to detect genetic deficiencies (deletions) for GST class T1. In male farmers with functional GSTT1 the odds ratio (OR) for association of PD with paraquat use was 1.5 (95 % confidence interval (CI): 0.6-3.6). In men with a deletion of GSTT1 the OR was 11.1 (95 % CI: 3.0-44.6; P interaction: 0.027). These findings suggest that PD risk from paraquat exposure may be extremely high when combined with a GSTT1 deficiency. Deletions of the GSTT1 gene are very common and occur in 20 % of the Caucasian population, presumably resulting in an enhanced neurotoxic effect of paraquat. Therefore a large number of individuals could be at a high risk of PD from toxicants such as paraquat via environmental exposure.

Lei et al 2014 – Paraquat impairs mitochondrial energy metabolism and induces loss of cell viability[91]

This study was conducted on dopaminergic neuroblastoma cells (SK-N-SH cell line, originally derived from a neuroendocrine tumor in bone marrow). Paraquat exposure induced the most profound alterations in the pentose phosphate pathway (PPP) by making it produce NADPH which generates reactive oxygen species. Paraquat blocked glycolysis, presumably by increased citrate accumulation via an impaired TCA cycle. It also induced a significant upregulation (over 25 %) in expression of several proteins including glucose-6-phosphate dehydrogenase (G6PD). G6PD is the rate-limiting enzyme of the PPP, and a major source of NADPH required by antioxidant pathways. Exposure of cells to paraquat, MPP+, and rotenone resulted in a decrease of total GSH (reduced glutathione) and its oxidized form, and this was accompanied by loss of cell viability. Perry and Yong (1986) observed that a decrease in GSH levels was one of the earliest biochemical changes in Lewy body disease, an asymptomatic precursor to Parkinson's disease. Paraquat induced a significant accumulation of GSSG (glutathione disulfide = oxidized GSH). This strengthens the hypothesis that paraquat impairs recycling of GSH via the glutathione reductase/NADPH cycle. Paraquat also impairs other antioxidant systems such as peroxiredoxins/thioredoxin/thioredoxin reductase. The study showed that changes in mitochondrial energy metabolism are specific to certain environmental toxins (paraquat) and contribute significantly to cell death.

Martin et al 2014 – Synergistic effect of paraquat and maneb on brain cells[92]

"Idiopathic Parkinson's disease (PD) may require 'multiple-hits' and disruption of more than one molecular pathway, by either environmental exposure or genetic variation (Sulzer, 2007). For example, in rodent models, the toxicity of paraquat to DA [dopaminergic] neurons is dramatically potentiated by maneb [...]. However, the mechanisms by which these and other agents interact remain obscure [...]. To address this question we have developed a chronic exposure model for paraquat and maneb neurotoxicity in the fly. [...] We have shown that under the chronic exposure conditions used here, paraquat and maneb combined, but neither paraquat nor maneb alone, cause DA cell loss at six weeks. We have further exploited this chronic exposure paradigm to show synergistic effects of maneb and ubiquitin E1 ligase inhibition. The interactions we observe may be relevant to human populations at risk for PD." [p. 351; p. 354]

Peng et al 2007 – Iron and paraquat accelerate neurodegeneration synergistically in sporadic parkinsonism[93]

"Extensive epidemiological data in humans and studies in animal models of Parkinson's disease (PD) suggest that sporadic forms of the disorder are not strictly genetic in nature but most likely because of combined environmental exposures over the period of the life-span coupled with increased genetic susceptibilities. Environmental paraquat and neonatal iron exposure have both been separately suggested as potential risk factors for sporadic forms of the disease. [...]" [p. 6914]

Results: Iron exacerbates paraquat-induced neurotoxicity in vitro. A signaling pathway based on the enzyme JNK [c-Jun N-terminal kinase] is involved in cell death induced by paraquat in combination with iron. Exposing newborn mice to iron led to a progressive age-related exacerbation of dopaminergic neurodegeneration caused by paraquat application. In mice, applying an antioxidant reduced death of neurons induced by iron and paraquat. Increases in oxidative stress in dopamine neurons (in the substantia nigra pars compacta) caused by the combined exposure to iron and paraquat were reduced by an antioxidant. In mice the JNK signaling pathway is activated more strongly in

the presence of iron versus paraquat alone, while this effect is reversed by an antioxidant ['EUK-189']. [pp. 6915-8]

"In addition to their direct neurotoxic effects, paraquat and iron may induce secondary effects that can contribute to neurodegeneration, including endogenous cellular iron release. Oxidative stress, such as that produced by paraquat and iron, can result in activation of inducible factors such as heme oxygenase (HO-1). HO-1 has been demonstrated to be induced in dopaminergic neurons both selectively in the SN [substantia nigra] of idiopathic Parkinsonian patients [...]." [p. 6920]

Qi, Miller & Voit 2014 – Models indicate that paraquat affects key enzyme for dopamine synthesis[94]

The altered profile of enzyme activities related to dopamine metabolism was analyzed mathematically, using both a model and statistical methods, to locate potential effects of paraquat and rotenone on dopamine into seperate cell compartiments (cytosol, vesicles, and synaptic cleft). Paraquat exposure was found to perturb fluxes associated with dopamine breakdown and its metabolites but did not seem to perturb dopamine fluxes in and out of the synaptic cleft. Without making any a priori assumptions regarding specific pesticide actions, Monte Carlo methods indicated that several specific mechanisms of pesticide neurotoxicity are likely and that an additional (inhibitory) effect of paraquat on tyrosine hydroxylase – the rate-limiting enzyme of dopamine synthesis – is a significant mechanism of paraquat toxicity, while activation of dopamine release from vesicles into synaptic cleft appeared to be secondary. The model accounted for other enzymatic regulatory processes.

Ritz et al 2009 – Gene-environment interaction between DAT gene variants and paraquat exposure (USA)[95]

This case-control study in agricultural areas in California investigated the interaction between genetic variability in the dopamine transporter protein DAT and exposure to maneb and/or paraquat. Paraquat and maneb had both been commonly used in the study areas. Data of mandatory reporting on use from 30 years were integrated into GIS models to estimate the past exposure of 324 patients diagnosed with Parkinson's disease (PD, "probable" or "possible" cases) between early 2001 and 2007. This was compared with the exposure to maneb and/or paraquat estimated for a control group; subjects were over 35 years old, had no PD, and had lived in the area for at least five years. Genotype variants for DAT (alleles) were determined in study participants, and genetic variability was found to modify the impact of exposure to maneb/paraquat. This can be considered as more compelling evidence that exposure is associated with Parkinson's disease. The DAT protein plays a central in neurotransmission as it is responsible for dopamine reuptake into brain cells. Shimizu et al (2003) hypothesized that DAT could act as a gateway into neurons for neurotoxicants including paraquat, however Richardson et al (2005) found DAT to be an unlikely transporter for paraquat.

Results: "High residential exposures to both paraquat and maneb between 1974 and 1999 increased the risk of PD more than 2-fold (adjusted OR, 2.32; 95 % CI, 1.23–4.40), and occupational exposure increased risk of PD by approximately 50 % (males: adjusted OR, 1.56; 95 % CI, 0.95–2.56). [...] When stratifying by levels of residential exposure to both maneb and paraquat, we found that high exposure increased risk almost 3-fold in subjects who carried one DAT susceptibility allele and as much as 4.5-fold in carriers of two or more susceptibility alleles (OR, 4.53; 95 % CI, 1.70–12.09). Yet, in those subjects with little or no residential exposure to these pesticides, we observed no indication of increase in risk with susceptibility allele carrier status or increasing number of susceptibility alleles [...]."

Discussion: "Most important in our study, risk of PD seems to depend on whether subjects are exposed to pesticides. We observed little indication that DAT susceptibility allele(s) affect risk in those unexposed to agriculturally applied maneb and paraquat or occupationally (albeit self-reported) exposure to any type of pesticide. For occupationally exposed males, we estimated an almost 3-fold increase in risk for those carrying two or more susceptibility alleles and a 2-fold increase in risk for those with only one allele, compared with those not carrying DAT susceptibility alleles. Our results thus replicate a strong gene–pesticide interaction (> 5-fold risk increase; [...]) previously reported for occupationally pesticide-exposed males (Kelada et al. 2006). Moreover, we employed our GIS-derived, record-based residential pesticide exposure estimates for maneb and paraquat and found that highly exposed subjects with one DAT susceptibility allele have an estimated 3-fold increase, and subjects with two and more alleles a 4.5-fold increase, in risk of PD compared with those with no DAT susceptibility alleles. There was little or no indication of a DAT susceptibility allele association in subjects with no or low residential pesticide exposure as estimated by our GIS model. [...]

In this region of California, our two pesticides of particular interest, maneb and paraquat, are both applied on common crops [...]. Pesticide drift can expose rural residents to pesticides without direct occupational contact."

Conclusion: "[...] Our genetic findings replicate a prior report (Kelada et al. 2006) and provide additional support for a gene–environment interaction between pesticide exposure and variants of the DAT gene."

Rodriguez-Rocha et al 2013 – Paraquat induces oxidative stress, mitochondrial inhibition, and cell death[96]

In human neuroblastoma cells, paraquat induced an increase in reactive oxygen species in the cytosol and mitochondrial matrix prior to cell death. It also activated transcription of redox-sensitive genes driven by antioxidant response elements (ARE) and nuclear factor kappa-B reporters. These results demonstrate a selective role of mitochondrial oxygen radicals in dopaminergic cell death induced by paraquat.

Roede, Hansen et al 2011 – Nerotoxic effects of paraquat caused via oxidative damage in mitochondria[97]

"In summary, the data presented here show MB [maneb] potentiation of PQ [paraquat] neurotoxicity does not occur by enhancing oxidative stress. The data provide little evidence of synergy or potentiation of the toxicity of one by the other. Instead,

Syngenta headquarters in Basel, Switzerland. Syngenta is the main seller of paraquat gobally, with an estimated market share of over 60%. | © lucarista/Shutterstock.com

the data show that PQ and MB act through different toxic mechanisms [...]. PQ induces ROS [reactive oxygen species] production affecting intracellular redox states, especially affecting mitochondria, whereas MB does not." [p. 374]

Shukla, Singh et al 2015 – NADPH oxidase mediates oxidative stress induced by paraquat in leukocytes[98]

The results of this study showed that the enzyme NADPH oxidase and impaired mitochondria regulate oxidative stress and antioxidant defense system in white blood cells (polymorphonuclear leukocytes) of rats exposed to maneb and/or paraquat. NADPH oxidase appears to partially regulate mitochondrial dysfunction in leukocytes. Inhibition of any of the complexes of the mitochondrial electron transport chain result in formation of reactive oxygen species (radicals) which can damage essential macromolecules and lead to cell death. Paraquat induces oxidative stress in exposed leukocytes and enhances inflammation, possibly also in organs not directly targeted.

Steenland, Wesseling et al 2013 – Increased risk of parkinsonism possibly linked to paraquat/maneb use (Costa Rica)[99]

Elderly patients in Costa Rica with past occupational pesticide exposure performed worse on common simple screening tests for neurologic disease, and the prevalence of Parkinson's disease in this group was much higher than expected. This may be partly explained by an increased risk among those who were exposed to pesticides (18 % of 400 patients). It is noteworthy that pararquat and maneb, which are implicated in development of some forms of parkinsonism, were widely used in Costa Rica since 1970 on coffee, the main crop in the area. [p. 100]

Tanner, Kamel et al 2011 / 2007 – Paraquat exposure associated with increased risk for parkinsonism (USA)[100]

In 2011, this case-control study included 110 patients with Parkinson's disease (PD) among the participants of the Agricultural Health Study in the USA. It found an increased risk of PD for exposure to paraquat (odds ratio = 2.5; 95 % CI: 1.4–4.7), a group of pesticide oxidative stressors including paraquat (OR = 1.7; 95 %CI: 1.0–2.8), and for exposure to rotenone and pesticides inhibiting complex I (an energy-transducing enzyme) in mitochondria.

A study in 2007 on the cohort of farmers from the Agricultural Health Study found elevated odds ratios (≥ 1.4) for prevalent PD cases (self-reported at enrollment) for three herbicides and three fumigants, considering only chemicals with four or more exposed cases. The odds ratios for prevalent PD were 1.5 for maneb/mancozeb, 1.8 for paraquat, and 1.7 for rotenone, while odds ratios for incident PD (identified during follow-up) were 2.1 for maneb/mancozeb, and 1.4 for paraquat (in the subset of applicators who completed a questionnaire); only one incident case had used rotenone. These results were based on four to ten exposed cases for each pesticide.

Uversky, Li et al 2002 – Paraquat increases aggregation rate of α-synuclein significantly[101]

In this study solutions of the brain protein α-synuclein were exposed to low pesticides concentrations [10–100 µM]. Certain pesticides in different chemical classes significantly stimulated the formation rate of fibrils (fine fibers) of α-synuclein. Paraquat and maneb were among the pesticides with the most significant accelerating effect, along with metal ions. Oxidative damage from free radicals which inhibit the mitochondrial Complex I and dopamine oxidation is often considered to be a causative factor in Parkinson's disease (PD). Alternatively, chemicals could directly affect aggregation of α-synuclein or adversely affect proteasomal function, leading to the accumulation and aggregation of α-synuclein. PD causation is likely to include both genetic factors and environmental agents. In this study, rotenone and paraquat had a direct effect on α-synuclein fibrillation, while MPP+ (MPTP) did not, although structures of MPP+ and paraquat are very similar and rotenone and MPP+ are known to be Complex I inhibitors. Rate of aggregation of a-synuclein induced by metal cations or pesticides may be increased via synergistic effects in the presence of other molecules. If pesticides such as herbicides or small soluble hydrophobic molecules (e.g. products of oxidative stress) are present in combination with certain metal ions, the concentration of either required to cause rapid formation of α-synuclein fibrils may be substantially reduced. Interactions between α-synuclein and environmental agents could play a role in pathological nigrostriatal degeneration and causation of sporadic PD. Thus total load of pesticides and metals in the brain, rather than individual levels, may be a key factor contributing to potential effects on α-synuclein fibrillation. Although the levels necessary to significantly accelerate α-synuclein fibrillation in our study were low (in the micromolar range), they decreased with increasing α-synuclein concentration. In tests on mice it was found that sufficient paraquat can enter neurons of the substantia nigra to cause α-synuclein to aggregate and form deposits (Manning-Bog et al 2002). Results in this study (in vitro) are paralleled by corresponding effects in studies *in vivo*.

Wang, Costello et al 2011 – Toxicity of paraquat to brain cells increases in combination with maneb (USA)[102]

"Combined ambient exposure to ziram and paraquat as well as combined ambient exposure to maneb and paraquat at both workplaces and residences increased PD [Parkinson's disease] risk substantially. Those exposed to ziram, maneb, and paraquat together experienced the greatest increase in PD risk. [...] The population-based case-control study of PD we conducted in a heavily agricultural region of California shows that combined exposure to ziram and paraquat, apart from maneb exposure, conferred an increased risk for developing PD. Our results suggest that exposure to paraquat, maneb and ziram may act together to increase the risk of PD more strongly than exposure to each individual pesticide alone or exposure to any combination of two pesticides. Only the early time window was important for ambient residential exposures to either ziram and paraquat or maneb and paraquat. In contrast, ambient work-place exposure during the early or late time window to either ziram and paraquat or maneb and paraquat increased PD risk, suggesting that although there may be a long induction period for these combinations of pesticides, potentially

more intense occupational exposures later in life may also contribute to risk of developing PD. Finally, younger participants consistently experienced the greatest risks when exposed to a combination of either maneb and paraquat or ziram and paraquat. We not only confirm our previous results for residential exposures to paraquat and maneb with our new occupational address based exposure measures (Costello et al 2009), but also observe that risk estimates at workplaces were generally larger than at residences and that exposures at both work places and residences together further increase risks." [p. 547; pp. 552-553]

Wu, Song et al 2012 – Central nervous system damage due to paraquat poisoning: neuroimaging study[103]

Using MRI / DTI imaging, Wu et al (2012) found significant abnormal signals in the brains of two patients (who been exposed to paraquat) during the acute post-poisoning phase, which indicated microstructural changes in extrapyramidal ganglia and hippocampus. These results are an indirect demonstration that acute paraquat neurotoxicity exerts a sustained effect during the acute and recovery stages of poisoning.

Exposure to multiple herbicides, or other pesticides

Dick et al 2007 – Increased parkinsonism risk related to multiple pesticide exposure[104]

A study of 959 prevalent cases of parkinsonism (767 with Parkinson's disease) and 1989 control subjects was conducted in Scotland, Italy, Sweden, Romania, and Malta. Lifetime and average annual exposures were estimated with a questionnaire and via job-exposure matrix, modified by modelling of subjective exposure. Exposure was measured as average annual intensity – derived by dividing the estimated lifetime cumulative exposure by the number of years of exposure to that chemical, expressed in units of the UK occupational exposure limit (OEL) for a typical pesticide (e.g. 0.5 denotes having worked at 50 % of the OEL for 240 days, 8 h per day for total number of years exposed). E.g. for tasks using herbicides in gardening (professional or hobby) the UK standard for paraquat (0.1 mg/m^3 8 h time-weighted average) was used. However, most participants could not indicate which pesticides they had been exposed to, while the average annual intensity tends to underestimate exposure owing to seasonal variations in pesticide use. Pesticide exposure was generally intermittent, both for recreational (4–8 days a year for an hour or less) and occupational applications (10–40 days a year; 4–8 h a day). There was an exposure–response relationship between pesticide exposure and parkinsonism (low exposure vs no exposure, OR=1.19, 95 % CI 0.90-1.57; high exposure versus no exposure, OR=1.56, 95 % CI 1.19-2.04). The median exposure to pesticides in the low exposure group was 0.0004 OEL units (range 0.0–0.003) and in the high pesticide exposure group the median exposure was 0.019 OEL units (range 0.003–0.89). With multiple logistic regression analysis the association was weaker. In conclusion this study provided important evidence of an increased risk of Parkinson's disease in relation to exposure to pesticides, suggesting that pesticide exposure may be a causative and potentially modifiable risk factor. [Paraquat was not directly specified.]

C) REVIEWS

Baltazar et al 2014 – How paraquat and maneb result in parkinsonism or Alzheimer's disease[105]

"[...] there is a growing body of epidemiologic evidence linking long-term/low-dose pesticide exposure to cancer, reproductive health issues, neurodegenerative diseases such as AD [Alzheimer's disease], PD [Parkinson's disease], and neurodevelopment impairments in children. Experiments concerning the environmental etiology of PD are more frequent than for other diseases, and several different animal models have been proposed. [...] Particularly, PQ [paraquat] and MB [maneb] exposure has been largely associated with PD. Other pesticides such as rotenone, dieldrin and diquat have also been shown to reproduce some features of PD in animal models. However, no single compound, including the non-pesticide MPTP, is able to reproduce all the hallmarks of human PD [...] Combined exposure to PQ+MB, or MPTP+PQ/MB yields potentiated damage to dopaminergic system, producing cell damage and loss, even when the doses of each compound are non-toxic. Most likely, PD might result from a prolonged contact to sub-toxic multi-hits at different targets within the dopaminergic system." [p. 86]

Mechanisms by which paraquat leads to the development of Parkinson's disease or other neurological syndromes include: Oxidative stress and inflammation; formation of reactive oxygen compounds; inhibition of ubiquitin-proteasome pathways (enzymes degrading misfolded, oxidized or aggregated proteins); and cell death of dopaminergic neurons (inducing certain forms of neurodegeneration).

Choi et al 2016 – Paraquat activates micoglia (brain cells) and alters dopamine metabolism[106]

"[...] substantial amount of evidence to suggest activation of microglia/astrocytes, altered dopamine metabolism, accumulation of alpha-synuclein and reduction of striatal dopamine levels as intermediate key events of paraquat exposure." [p. 74]

Dagda et al 2013 – Paraquat inhibits mitochondrial function, impairs autophagy, blocks neuronal dopamine release[107]

"Mechanistically, paraquat *inhibits mitochondrial oxidative phosphorylation and blocks the release of dopamine from synaptic terminals* prior to neurodegeneration (Tawara et al 1996; Takamura et al 2008). However, unlike other PD [Parkinson's disease] toxins, paraquat toxicity robustly *promotes protein aggregate formation and genetically interacts with α-synuclein* to exacerbate PD pathology in vivo (Manning-Bog et al 2003, 2002). Paraquat-induced increases in α-synuclein aggregate levels is likely due to *impairment of autophagic flux* [...] These results and our unpublished observations suggest that *mitochondrial ROS [reactive oxygen species] elicited by paraquat blocks autophagy* both in *vitro* and *in vivo* (Janda et al 2013). [...] Future studies are required to identify the molecular players downstream of JNK1 [c-JUN N-terminal kinase-1, an enzyme] that regulate paraquat-mediated autophagic flux. [...]

The *number of pesticides, and their concentration and combinations should be thoroughly regulated*. Since exposure is directly

correlated with duration, *there should be a limit on the number of hours a day spent spraying pesticides.* Furthermore, relocation programs supported at the local or state level should allow susceptible high risk populations to move from geographical locations harboring large chemical plants to safer areas [...] In summary, an increased chronic exposure of humans to PD toxins along with interactions with certain genes and aging can increase the risk of developing PD." [pp. 22176, 22179]

Franco et al 2010 – Mechanistic aspects of neuronal cell death induced by paraquat[108]

"To date, the molecular mechanisms involved in neuronal cell death by paraquat are still unclear. Research so far clearly demonstrates a role for oxidative stress and ROS in paraquat-induced neurotoxicity, which seems to be mediated by both mitochondrial and ER stress pathways. [...] it has been demonstrated that exposure to paraquat together with other pesticides (maneb) or metals (iron) exert their toxicity by mechanisms involving synergistic processes or the activation of completely different signal transduction pathways."

Jones, Huang et al 2014 – Varying genetic susceptibility to paraquat neurotoxicity may be mediated by iron[109]

Many neurodegenerative diseases can be classified as familial versus sporadic. Familial forms usually appear at an earlier stage in life and can be highly heritable. Conversely, causes of sporadic neurodegenerative diseases are far more complex and almost certainly involve interactions between genetic and environmental factors (Kieburtz & Wunderle 2013). Sporadic Parkinson's disease (PD) is more prevalent in rural areas than in urban areas and most likely results from gene–environment interactions. Exposure to pesticides is more common in rural areas; additionally well water used for consumption ranges widely in iron concentration. Iron homeostasis involves many proteins and their expression varies widely in different individuals. The authors hypothesize that iron may be an important factor in the neurotoxicity of paraquat and that a system genetics approach can help to elucidate some of the critical mechanisms. Although the interaction of genetic and environment factors is widely thought to be important for sporadic PD, it has created a complex experimental template. [pp. 191, 195]

Moretto & Colosio 2011 – Combined exposure to paraquat/pesticides enhances symptoms of Parkinsonism[110]

Toxicological evidence suggests that, under certain conditions and to a varying degree, paraquat, maneb and other dithiocarbamates, pyrethroids, rotenone, and dieldrin have neurotoxic effects consistent with a potential role in the development of a PD syndrome in animal tests. So far no single chemical is known to reproduce all characteristics of human PD. This might result from multiple sub-toxic hits at targets in the dopaminergic system over a long period, accelerating neuron loss due to ageing and appearance of clinical PD symptoms in previously exposed individuals. Combined effects of e.g. maneb and paraquat suggest the highly sensitive dopaminergic system may be damaged by cumulative lesions at different sites, or through changes in availability of a certain toxicant at the site of action. Paraquat is eliminated from the brain much more slowly than from the liver, thus a single high dose of paraquat may have longer-lasting effects in the brain. Additive or synergistic effects of other pesticides can therefore occur after initial exposure. This aspect is relevant as paraquat, maneb and pyrethroids are still widely used in many parts of the world. The available data on measured or estimated exposures, when compared to data derived from experiments on animals, did not support a correlation between actual pesticide exposure and development of PD in humans. The relevance of doses used in tests remains an issue. [pp. 388-9]

Pezzoli & Cereda 2013 – Meta-analysis finds twofold increase in risk of Parkinson's disease associated with exposure to paraquat[111]

Prospective cohort studies and case-control studies providing risk estimates relating Parkinson's disease (PD) to exposure to pesticides or solvents, or to proxies (proxy variables) of exposure, were analyzed. A total of 104 studies (3,087 citations) fulfilled inclusion criteria for meta-analysis. In prospective studies, PD was associated with farming and the association with pesticides was highly significant in the studies in which PD diagnosis was self-reported. In case-control studies, study quality appeared to be a source of heterogeneity in risk estimates for some exposures. In case-control studies, PD risk was associated with exposure to any type of pesticides, herbicides, insecticides, and solvents; risk increased by between 33 % and 80 %. No association was observed with fungicides, rodenticides, organochlorines, and organophosphates. About a twofold increase in risk was observed for exposure to paraquat, while no association was found with exposure DDT, maneb or mancozeb. PD was also associated with proxy conditions for exposure (occupation or rural living), and risk increased by about 30-34 %. Results also support an involvement of maneb and mancozeb or other chemicals in this group.

Conclusions: The literature supports the hypothesis that exposure to pesticides or solvents is a risk factor for PD. Further prospective and high-quality case-control studies are required to substantiate a cause-effect relationship. Studies should also focus on specific chemicals and route of exposure. Some compounds have been withdrawn from the market in industrialized countries, however they are still in use in developing countries. [pp. 2037, 2040]

EXPOSURE TO MULTIPLE PESTICIDES

Parrón et al 2011 – Increased risk for neurodegenerative diseases in areas with high pesticide exposure[112]

Epidemiological study in Andalusia, Spain. Prevalence rates for Alzheimer disease, Parkinson's disease, multiple sclerosis, and suicide attempts were significantly higher in districts with a high level of exposure to pesticides in the environment, compared to districts with lower exposure. Herbicides used in the area include paraquat and diquat. Odds ratio for Parkinson's disease associated with living in high exposure area was 1.3 (95 % CI 1.22, 1.39) ($p < 0.001$); for Alzheimer's disease it was 2.1 (95 %

CI 1.96, 2.25) ($p < 0.001$); and for attempted suicide it was 1.87 (95 % CI 1.67–2.08) ($p < 0.001$); for other neurodegenerative diseases it was not elevated or significant.

Sade et al 2015 – Proximity to agricultural fields and field size contribute to risk for Parkinson's disease[113]
In this population based study standardized incidence rates for Parkinson's disease were found to be higher than expected in rural localities. Additionally it appears that proximity to agricultural cultivated fields and the field size contributed to increased risk. [Paraquat was not directly specified.]

Searles Nielsen et al 2015 – Increase in α-synuclein blood levels of workers during spray season[114]
Alpha-synuclein is a protein that is critically involved in Parkinson's disease (PD). Three of four workers experienced substantial increases of α-synuclein levels in blood during the spray season. However, this finding is somewhat difficult to interpret as it is not known to which extent blood level of α-synuclein indicates levels in the brain or PD risk and as levels can fluctuate markedly within an individual over time. [Paraquat was not specified.]

Van Maele-Fabry, Hoet et al 2012 – Studies find pesticide exposure linked to risk increase for PD[115]
A meta-analysis was conducted of 12 studies (chosen from 175 studies) on occupational exposure to pesticides and Parkinson's disease. The calculated meta-rate ratio for all included studies was 1.28 (95 % CI: 1.03-1.59), but inconsistency among the twelve relative risk estimates of individual studies and high heterogeneity complicated analysis. Data allowed to distinguish by type (insecticides, herbicides, fungicides) for herbicides and fungicides, and by specific pesticide only for paraquat, yielding non-statistically significant risk modifications. Consistency was observed among studies on herbicides, while for fungicides the heterogeneity between studies remained high. Distiguishing by occupation involving potential exposure ('farming only' or 'working in plantations') resulted in consistency among studies for plantation workers and the estimated relative risk was statistically significantly increased for these. The meta-rate ratio was also increased for the other group but not statistically significant.

Overall results suggest an association between occupational exposure to 'pesticides' and Parkinson's disease (PD). The observed risk was increased by 28 % (statistically significant). When omitting studies with extreme weight values this did not vary substantially, supporting the hypothesis that exposure to pesticides increases risk of PD. Studies were too scarce to allow a conclusion for specific chemical classes of pesticides. Only two of the studies analyzed referred to paraquat specifically: Engel et al (2001) [20 exposed PD cases among 65 PD cases in a cohort of 310 orchardists (238 exposed, 72 non-exposed), RR 0.8 (95 % CI 0.5–1.3)], and Tomenson & Campbell (2011) [mortality (underlying cause of death) among 926 male factory workers who had worked in paraquat production, 1 PD death among 292 deaths, "insufficient sampling to perform a quantitative exposure assessment"]. [pp. 32, 35, 37, 41]

van der Mark et al 2012 – Exposure to herbicides and insecticides increases risk of Parkinson's disease[116]
Meta-analysis of thirty-nine case–control studies, four cohort studies, and three cross-sectional studies. A positive association of Parkinson's disease was observed with herbicides (summary risk ratio of 1.40; 95 % CI 1.08–1.81) and with insecticides (summary risk ratio of 1.50; 95 % CI 1.07–2.11), but not with fungicides. This is in line with conclusions of Brown et al (2006). However, it is difficult to disentangle the effect of herbicides and insecticides given that use of these two pesticide groups is often highly correlated. Overall summary risk estimates strongly suggest that exposure to pesticides, and to herbicides and/or insecticides in particular, increases the risk of developing Parkinson's disease. [Paraquat was not directly specified.]

2.3 – DERMAL TOXICITY AND DERMATITIS

Besides skin irritation and dermatitis (chronic inflammation of skin), paraquat was also found to cause skin cancer (section 4.6). Skin damage strongly facilitates absorption of paraquat and increases risk of poisoning.

Black AT, Gray et al 2008 – Paraquat exposure induces oxidative stress in skin cells[117]
In cultures of mouse skin cells (keratinocytes) paraquat readily induced oxidative stress by producing reactive oxygen intermediates. These lead to increased oxidation of proteins, particularly in differentiated skin cells, and upregulation of enzymes with antioxidant activity. However, the role of cell differentiation in regulating the expression of antioxidant enzymes and in determining how this process controls responses of the skin to oxidative stress due to paraquat is not yet fully understood. [pp. 8-9]

Paolillo, Piccirilli et al 2011 – Upregulation of genes responsible for inflammation or death of skin cells[118]
In human skin cells exposed to paraquat, specific genes were activated which are involved in inflammatory responses and genes regulating cell death (apoptosis) or the breakdown of proteins (proteolysis). Paraquat produced a similar pattern of activation of several genes involved both in inflammation and apoptosis.

Xu, Wang et al 2015 – First case of toxic epidermal necrolysis related with paraquat poisoning (China)[119]
"We describe 2 paraquat-poisoned patients with TEN [toxic epidermal necrolysis]. Both patients presented erythema after hospital discharge following initial paraquat poisoning and then developed a widespread eruption of diffuse erythema on almost the whole body, with bullae, epidermal necrosis and sloughing. They were successfully treated. [...] It is suggested that both skin exposure and ingestion of paraquat could induce TEN. To our knowledge, this is the first case report of TEN related to paraquat poisoning. [...] In summary, paraquat, as a causative factor of TEN, should be highly considered as drug causality when suspicious clinical eruption emerges after paraquat poisoning [...]" [p. 209, 211]

2.4 – IMPAIRED LUNG FUNCTION

Cha, Lee et al 2012 – Possible association between paraquat application and respiratory health effects among South Korean farmers [120]

This study investigated the association among farmers between occupational paraquat exposure and respiratory health effects. Researchers conducted a cross-sectional survey of 2882 full-time farmers in South Korea. Data collection included a questionnaire and spirometry testing. Logistic regression analysis and linear regression analysis were performed to evaluate the relationship between paraquat exposure and respiratory health outcomes after adjustment for potential confounders. The risks of self-reported physician-diagnosed asthma, chronic obstructive pulmonary disease and allergic rhinitis were non-significantly increased among paraquat-applying farmers compared with non-paraquat-applying farmers. Although the results of a pulmonary function test fell within normal limits, a decline in forced vital capacity and forced expiratory volume in one second was apparent among paraquat-applying farmers compared with non-paraquat-applying farmers. The findings suggest a possible association between paraquat application and adverse respiratory health effects among farmers.

de Jong, Boezen et al 2014 – Exposure to pesticide linked to accelerated long-term decline in lung function (Netherlands)[121]

This prospective cohort study on the epidemiology of pulmonary diseases included 2'527 subjects from the general population in a rural area and an urban in the Netherlands. It was started in 1965 and participants were followed for 25 years, with surveys performed every 3 years. One-third of the subjects (33 %) had been occupationally exposed to high levels of vapors, gases, dusts and fumes (VGDF), while 12 % had been exposed to high levels of pesticides. Occupational exposure to high levels of multiple pesticides – both herbicides and insecticides – was negatively associated to annual change in lung function. This effect was confirmed when an estimate of cumulative pesticide exposure (intensity-years) was used, and after adjustment for co-exposure to VGDF and interaction with smoking. Pesticide exposure, in the last-held job and as a cumulative measure, was associated with accelerated decline in forced expiratory volume in 1 second (FEV1) and FEV1 as % of inspiratory vital capacity. Annual change compared with no exposure was significantly larger in 'ever smokers', where an excess change in FEV1 of −6.9 mL/year (95 % CI: −10.2, −3.7) was associated with high pesticide exposure. This shows that occupational exposure to pesticides is associated with clinically relevant accelerated annual decline in the lung function. This may subsequently increase the risk for developing chronic obstructive pulmonary disease (COPD) and thereby contribute to the large burden of morbidity and mortality associated with this disease. Subjects who were highly exposed to pesticides included field crop and vegetable growers (72 %), mixed crop and animal producers (12 %), gardeners, horticultural / nursery growers (15 %), and tree and shrub crop growers (1 %). Associations between high pesticide exposure and annual change in the lung function (FEV1 and FEV1 as %VC) were stronger in a subgroup of gardeners and horticultural or nursery growers. The pesticide subcategories 'insecticides' and 'herbicides' were analysed separately. Associations with 'insecticides' were similar to those for 'all pesticides'. However, the strongest association with FEV1 was seen for low exposure to 'herbicides', an association that may have been driven by gardeners and horticultural and nursery growers.

During the 1960s and 1970s, the majority of cultivated crops were cereals (about 50 %), and during the 1980s and 1990s they were potatoes (about 50 %). Within the potatoes sector, dinitrophenol herbicides were used until the 1980s. However, from the early 1980s onward diquat and paraquat became the most commonly used herbicides (M. Brouwer, University of Utrecht, personal communication, 2014; see details in Web Tabe 4). The primary mechanism for paraquat toxicity is oxidative damage to lungs tissue via radical generation. Exposure to such a pesticide is likely to be more pronounced when physiological antioxidant systems are consumed and the lungs have been irritated by tobacco smoke. Pesticides such as paraquat may then act synergistically with smoke, as suggested by an interaction between smoking and pesticide exposure found in a previous cross-sectional study (de Jong et al 2014) and in the current longitudinal study.

Dalvie et al 2009; 1999 – High use and long-term respiratory effects of paraquat noted in South Africa[122]

"Paraquat, amongst the highest quantities of active ingredients and ATI [acute toxicity indicator] sold in total and per hectare in 1999, has been found to be associated with long-term respiratory defects amongst Western Cape farm workers (Dalvie et al, 1999)."

Dalvie et al (1999) found a significant association between the long-term exposure of workers (who had been spraying paraquat) with desaturation of arterial oxygen during maximum exercise, in a dose dependent fashion.

Hernández et al 2008 – Lung dysfunction among greenhouse workers spraying pesticides in Spain[123]

This study in Granada (Spain) included 114 agricultural workers from an area with intensive cultivation in greenhouses. Of the participants, 89 'sprayers' were engaged in agricultural tasks for the whole year, including pesticide application to crops. The other 25 subjects were farm workers from the same area who had used no pesticides (nonsprayers – control group), broadly matched for age, BMI, and smoking habit. The 10 pesticides or chemical groups most commonly used during the growing season were: neonicotinoid insecticides (used by 81.5 % of sprayers), oxadixyl (80.2 %) and oxythioquinox fungicide (74.1 %), abamectine (71.6 %), phenylureas (69.1 %), organophosphates (54.3 %), dithiocarbamates (54.3 %), carbamates (45.7 %), endosulfan (28.4 %), and bipyridilium herbicides (25.6 %, paraquat and diquat). Fourteen subjects (12.3 %), all of whom were sprayers, had previously experienced poisoning by pesticides. Among sprayers, 24.7 % regularly used personal protective equipment (PPE) during mixing/loading of pesticides and 47.5 % used PPE during application of diluted spray

mixture inside greenhouses. Symptoms reported by participants which can be attributed to pesticide exposure included 45.9 % nonspecific symptoms, 33.0 % respiratory symptoms, 37.6 % irritative symptoms, and 42.2 % other symptoms related to pesticides. Lung functional measures were compared with acute symptoms. The diffusing capacity of the lungs for carbon monoxide (TLco/va) was significantly reduced in subjects showing nonspecific symptoms and marginally reduced in those with respiratory symptoms. A significant decrease in the forced expiratory flow FEF25–75 (between 25 and 75 % of forced vital capacity) was observed in subjects with respiratory symptoms. Cumulative exposure to pesticides was a significant risk factor for reduction in FEF25–75, and exposure to paraquat or diquat was associated with a decrease in the diffusing capacity of the lungs. In the region extensive use of pesticides results in numerous acute intoxications each year. Between 2000 and 2006, 595 acute pesticide poisonings were reported to the Epidemiological Surveillance Program of Almería; 80.5 % of cases had an occupational origin. Exposure to paraquat or diquat was associated with a decrease in the lungs' diffusing capacity for CO. This indicates possible subtle changes of the alveolar capillary membrane among paraquat/diquat handlers which could lead to abnormalities in pulmonary gas exchange observed in earlier studies (Schenker et al 2004; Yamashita et al 2000). It was not clear whether this decrease in the gas transfer factor is transient or persistent. This study demonstrated that workers who are exposed to pesticides on an acute basis or long-term are at an increased risk of developing significant changes in respiratory function and clinical symptoms. Although there was a certain degree of lung dysfunction, it is not clear whether these adverse effects could cause a clinically significant obstructive or restrictive lung disease or chronic impairment of gas exchange. The underlying mechanism may be an irritant effect of the spray droplets, aerosol or vapour of paraquat or other pesticides on sensory nerves in the airways and alveolar capillaries. However it may also be an immuno-allergic response, or result from oxidative stress induced by chronic exposure. [pp. 840-48]

Valcin, Henneberger et al 2007 – Chronic bronchitis among nonsmoking farm women exposed to paraquat (USA)[124]

Data from nonsmoking farm women in the Agricultural Health Study in the USA were assessed with regard to occupational risk factors for chronic bronchitis. Five pesticides including paraquat were associated with an increased risk for chronic bronchitis after adjustment for age, state, and related agricultural exposures.

Yamashita et al 2000 – Survivors of paraquat poisoning suffer long-term restrictive dysfunction of lungs (Japan)[125]

These results indicate that survivors of paraquat poisoning may be left with a restrictive type of pulmonary dysfunction and suggest that a long-term follow-up of lung function may be necessary.

2.5 – DEPRESSION RELATED TO EXPOSURE TO PESTICIDES, INCLUDING PARAQUAT

Kim, Ko et al 2013 – Occupational pesticide poisoning among farmers and depressive symptoms (South Korea)[126]

This study in South Korea investigated the association between occupational pesticide exposure and depressive symptoms among male farmers, for which there has been only limited evidence. A nationwide sampling survey of male farmers was conducted in relation to an oil spill in 2011. From this 1958 male farmers were interviewed in relation to depression and pesticide exposure, including paraquat exposure. Severity of occupational pesticide poisoning was evaluated according to symptoms, types of treatment and number of pesticide poisonings per individual. Depressive symptoms were assessed using the Geriatric Depression Scale. Among total farmers, 10.4 % (n=197) reported depressive symptoms. After controlling for potential confounders, occupational pesticide poisoning in the previous year was positively associated with the risk of depressive symptoms (OR=1.61; 95 % CI 1.10 to 2.34). Cases of more severe pesticide poisoning, such as moderate- or severe-symptom cases (OR=2.81; 95 % CI 1.71 to 4.63), outpatient or hospitalisation cases (OR=2.52; 95 % CI 1.15 to 5.53), and multiple poisoning cases (OR=1.82; 95 % CI 1.19 to 2.76) showed higher risks of depressive symptoms than did milder cases. Among the pesticides causing the poisonings, paraquat dichloride was found to be a significant predictor of depressive symptoms. The findings suggest that the risk of depression appears to be related to the severity of symptoms of poisoning, type of care received and the number of previous episodes of acute poisonings. The use of manual backpack sprayers showed a higher risk for depressive symptoms than non-use. The authors emphasized a need for timely intervention for reducing pesticide poisoning through restrictions on certain pesticides. [pp. 304-5, p. 308]

Lin, Yen et al 2014 – High mortality in patients with mood disorder: paraquat exposure cause or effect? (Taiwan)[127]

"Mood disorders (54.0 %), including dysthymic (26.7 %) and major depressive disorders (24.7 %), were the most common psychiatric diagnoses among the self-poisoning patients. [...] We identified 157 patients who were admitted [to a tertiary general hospital in Taiwan] after attempting suicide by paraquat poisoning during 2000 to 2010. [...] Dysthymic disorder remained the only psychiatric diagnosis to independently predict mortality (OR = 5.58-, 95 % CI: 1.13–27.69; p<0.05). [...] During the 10-year enrollment period, we found that the cause of paraquat poisoning in 87.8 % of presenting patients was attributable to attempted suicide. This is similar to the nearly 90 % rate in Japan (Nagami et al 2007) and the 73.4 % rate in Korea (Seok et al 2009). [...] One common scenario in suicide attempts by paraquat self-poisoning is impulsive paraquat intake following family conflict (Mishara 2007). In line with prior studies (Hutchinson 1999; Mishara 2007), the precipitants of suicide in our study centered on intra-familial conflicts. Accordingly, it was postulated that the high fatality of pesticide suicide was due to its high lethality, which renders fatal even the attempts of those with low suicidality, and not due to inadequate treatment of mental illness (Bertolote et al 2006). [...] Another

important finding is that after adjusting for medical factors, dysthymic disorder was associated with a high risk of mortality. [...] Also, more studies are needed to verify whether a causal link exists between paraquat exposure and subsequent depression, similar to that of organophosphate (London et al 2005). Longitudinal prospective studies to compare the mental status prior to and after chronic paraquat exposure may be required to answer this hypothesis. In conclusion, faced with the rampant destruction paraquat unleashes on tens of thousands of lives worldwide, we cannot stress enough the importance of restricting access to paraquat (Phillips & Gunnell 2009). In the practice of suicide prevention (Mann et al 2005), primary care physicians and gatekeepers should be aware of chronic depressed patients' accessibility to paraquat. On the other hand, those who have high accessibility to paraquat may get a screen for depression." [pp. 1-3, 5]

EXPOSURE TO MULTIPLE PESTICIDES

Parrón et al 1996 – Increased suicide rate in area with high use of pesticides; Almería, Spain[128]

El Poniente in eastern Almería, Spain, has an extremely high density of greenhouses where pesticide use is very intensive. Data on mental health for 1992 reveal that the incidence of mood disorders in the area of El Poniente was statistically higher than in the Levante area ($P < 0.001$, OR: 1.88, confidence interval: 1.42-2.49). In addition to other risk factors continued exposure to pesticides may influence mood disorders. The majority of victims where the cause for attempted suicide could be established had a depressive episode immediately before death. Some suicides occurred in persons with no reported severe depressive symptoms but a mood swing or an unrecognized depressed state cannot be ruled out. While the higher suicide rate in El Poniente is not well understood, the easy access to pesticides and lacking knowledge of farmers about their high toxicity may have contributed to the fatal outcome of impulsive suicidal acts. Bearing in mind that Huercal-Overa, another agricultural area in Almeria with a higher proportion of farmers than El Poniente, had a lower use of pesticides (due to the crops grown) it appears plausible to assume a possible strong association between suicides and pesticide exposure. The authors (Parrón et al 2011) noted that paraquat and diquat were used in western, central, and eastern Almería – the study region.

Pickett, King et al 1998 – Suicide risk increased in farmers spraying multiple pesticides (Canada)[129]

In a Canadian cohort of farmers the risk of suicide deaths was statistically significantly increased among those farmers who had applied herbicides and insecticides, compared to non-sprayer farmers (odds ratio= 1.71, 95 % CI = 1.08–2.71). [Paraquat was not directly specified.]

2.6 – IMMUNOTOXICITY AND GENOTOXICITY/CANCER

Avilés I. 2007 – DNA damage in pesticide merchants exposed to multiple pesticides including paraquat[130]

Potential genetic damage associated with exposure to multiple pesticides was evaluated among Nicaraguan pesticide merchants in the Central American region (working at agrochemical dispensiaries, so-called 'agro-servicios'). In mucosal cells taken from the mouth micronuclei were used as a biomarker. Cytogenetic effects occurred among merchants who were occupationally and chronically exposed to a mixture of pesticides. The authors found that the following pesticides were implicated with a genotoxic effect in workers: metamidofos, endosulfan, paraquat, parathion, and 2,4-D. [pp. 7, 82]

Hassuneh, Albini & Talib 2012 – Acute subtoxic paraquat dose within MRL range induces immunotoxicity[131]

This study assessed the impact of a single acute oral dose of paraquat on the immune system of BALB/c mice, at 2, 4, and 20 mg/kg. Hematologic toxicity was not observed, but a marked reduction of proliferative responses in both T and B lymphocytes was detected and also a significant reduction of IgM plaque-forming cell (PFC) counts. Reduced PFC numbers at the low dose of 2 mg/kg are a strong indication of immunotoxicity. Responses of B cells to sRBC antigen (whole sheep blood) were also significantly inhibited. This acute immunotoxicity at 2 mg/kg is alarming, as it is below current acute oral doses of no-observed-adverse-effect level (NOAEL). At concentrations of 0.006 µg/mL, equivalent to the acceptable daily intake (ADI) dose of 6.0 µg/kg set by FAO/WHO, paraquat induced a proinflammatory TH17 (T helper) cytokine profile, evidenced by the up-regulation of several cytokine genes, including the interleukin 17 family, in the presence of paraquat in mouse splenocytes in vitro activated by phytohaemagglutinin (mitogen blastogenesis assay). This indicates that at higher concentrations paraquat can deplete immune functions, while lower doses could alter immune responses toward a proinflammatory profile such as that of TH17 cells. These have been strongly implicated in various autoimmune diseases such as multiple sclerosis, psoriasis, autoimmune uveitis, juvenile diabetes, rheumatoid arthritis, and Crohn's disease (Stockinger & Veldhoen 2007). The data presented in this study suggest that regulatory measures for paraquat need to be revised and implemented in countries where there is no ban or restriction of paraquat. Considering that the maximum residue levels (MRLs) for paraquat established by FAO and WHO for certain food and animal feed crops range between 0.005 and 10.0 mg/kg, these findings stress the importance of applying strict regulations on the use of paraquat as an herbicide.

Lim, Won et al 2015 – Paraquat reduces natural killer cell activity with immunosuppressive effect[132]

The results showed that treatment of splenocytes (natural killer cells) of mice with paraquat led to increased metallothionein expression in several organs (liver, kidneys, testes) and in splenocytes, caused a reduction of both free zinc ions in sera and in free intracellular zinc, and reduced the expression of GATA-3, a zinc-finger transcription factor important for maturation and activity of T-cells and natural killer cells. These results provide a basis for a new molecular mechanism to describe potential immunosuppressive effects of paraquat in vivo.

Okabe, Nishimoto et al 2010 – Paraquat perturbs immunoglobulin productivity in mouse lymphocytes[133]
The immunotoxic potential of paraquat was tested on mouse splenocytes (white blood cells including B and T lymphocytes) cultured in vitro. Paraquat at 10-4 to 10 µM decreased productivity of immunoglobulin M (IgM) significantly. It had the same effect on immunoglobulin G (IgG) productivity at levels as low as 10-7 to 10-6 µM, while IgA was unaffected. At higher concentrations of 10-100 µM paraquat, on the other hand, no such effect was observed, although human lymphocytes die at 100 µM. So far the impact of paraquat at lower doses is not understood. After exposing mice to paraquat (0.1 %, 1 % or 4 % of LD50) daily for two weeks IgM was significantly decreased at the high dose, and IgG were slightly lower after four weeks at high dose (not significant). IgA levels increased at low and medium dose after four weeks. Results suggest that paraquat perturbs immunoglobulin productivity of mouse lymphocytes in a manner which depends on the immunoglobulin class. The decrease of immunoglobulin M caused by paraquat poses a risk as this implies a compromised immune system. This effect and perturbation of other immunoglobulins (IgA and IgG) suggest that studies are required to assess potential health risks resulting from residues of paraquat in crop plants consumed as food. [pp. 258-9, 262]

Van Osch et al 2010 – Mutations more frequent in skin cells of mice exposed to paraquat[134]
Acute exposure to paraquat resulted in a 1.6-fold increase in the mutation frequency in the skin of wild-type mice, compared to spontaneous mutations (control group). Mutation frequency was also elevated in harlequin disease mice which are very susceptible to oxidative stress. However, the pattern of independent mutations was similar to that in wild-type mice and the impact on harlequin disease mice was not considered significant. However, microdeletions with microinsertions were observed in DNA of skin cells from wild-type mice exposed to paraquat. As this type of mutation may be an important contributor to cancer (Scaringe et al 2008) the authors called for more studies on similar mutations in skin and their association with paraquat exposure. [pp. 239-240]

Further publications referring to genotoxicity of paraquat:
Anderson & Scerri 2003; Bowra et al 1982; D'Souza et al 2005; Engel et al 2005; Jee et al 1995; Lee et al 2005; Marrs & Adjei 2003; Monge et al 2007; Wesseling et al 1999 & 1996 (see references in section 7.4 below)

EXPOSURE TO MULTIPLE PESTICIDES

Samanic, De Roos et al 2008 – Increased risk of brain tumor in women exposed to multiple herbicides (USA)[135]
Case-control study. Women who reported having used 'herbicides' had a significantly increased risk for meningioma (a brain tumor) compared with women who never used herbicides (odds ratio = 2.4; 95 % CI: 1.4, 4.3), and there was a significant increase in risk with increasing years of herbicide exposure and increasing cumulative exposure. There was no association between meningioma and herbicide exposure among men. [Paraquat was not directly specified.]

Wigle, Turner et al 2009 – Childhood leukemia and parental exposure to multiple herbicides[136]
Paternal occupational exposure to multiple herbicides was associated with an increased risk of childhood leukemia (summary odds ratio = 1.25; 95 % CI, 0.94–1.66); however, the few relevant studies did not address exposure–risk relationships and a firm conclusion was not possible. The association between risk for childhood leukemia and prenatal maternal occupational exposure to herbicides (summary OR = 3.62; 95 % CI, 1.28–10.3) was moderately strong, based on few available studies. [Paraquat was not specified.]

2.7 – REPRODUCTIVE TOXICITY AND KIDNEY DAMAGE

Hossain, Ali et al 2010 – Declines in semen quality among paraquat-exposed farmers in Malaysia[137]
"A cross-sectional study was conducted among male farmers from 3 different communities in Sabah, Malaysia. A total of 152 farmers participated in this study of whom 62 farmers had been exposed to either paraquat [39 farmers] or malathion [15 farmers] or both [8 farmers] to varying extents. The association between pesticide exposure and semen parameters was highly significant. [...] The results showed a significant decline in semen quality with a decline in sperm count, motility and higher percent of teratospermia among subjects with pesticide exposure, and those who were exposed to pesticides had significantly 3 to 9 times greater risk of having abnormal semen parameters. [...] In conclusion, this study confirmed that farmers exposed to pesticides, such as paraquat and malathion, exhibit a significant decline in sperm concentration and motility with an increase in sperm abnormality." [pp. 353, 359]

McClean, Laws et al 2010 – Paraquat exposure possibly linked to kidney damage in agricultural workers[138]
"Herbicides account for approximately 95 % of the agrichemicals used at ISA [Ingenio San Antonio], as weeds pose the biggest risk to sugar cane production. [...] Of these chemicals that may have been used at ISA in the past, the information obtained during this initial review indicated that there is a potential for kidney damage associated with exposure to paraquat, MSMA, diazinon, warfarin, and DBCP (nemagon). However, of these five chemicals, representatives of NSEL [Nicaragua Sugar Estates Limited] were only able to confirm the previous use of paraquat and warfarin. [...] Regarding the potential for exposure to a given chemical to be associated with acute kidney damage, the results of the literature review indicated that two of the 36 agrichemicals (2,4-D and paraquat dichloride) have strong evidence of an association [...] Regarding the potential for an association with CRI [chronic renal insufficiency] specifically, we found only limited evidence (beyond the unproven hypothesis that any kidney damage may eventually result in CRI)." [pp. 21, 29, 44]

3

Self-harm and paraquat – preventive action urgent

3.1 – SYNOPSIS

Ingesting pesticides is a frequent means of self-harm, particularly where they are readily available and accessible. High fatality rates are predominantly due to the very high acute toxicity of particular pesticides such as paraquat, endosulfan, certain organophosphates or carbamates and other acutely toxic pesticides. Paraquat is one of the most commonly used pesticides for self-harm. There is no antidote and no treatment has proven to be reliable (see 3.7). Thus ingesting paraquat is almost always fatal, particularly in rural and other areas with limited medical services. It is rarely an immediate death and can be slow and very painful.

In many instances an action to cause self harm is an immediate response to a personal crisis rather than an intention to commit suicide. Self harm can be a cry for help, result of depression, or act of desperation; and it may often be difficult to distinguish cases of self-harm from homicide or severe accidental exposure.

A retrospective study in South Korea on patients who attempted suicide by ingesting paraquat found impulsive intake due to personal conflict, e.g. with family members, was a common scenario. Mood or depressive disorders were factors that increased mortality significantly. The authors pointed out that it was not clear whether depression was a consequence of previous paraquat exposure (Lin et al 2014). Other studies have found that exposure and use has been linked to depression and thus can in itself lead to self-harm (London et al 2005). Furthermore, the economic burden of suicide is largely not recognized as these are predominantly indirect costs due to premature deaths (Choi et al 2012). The impact on families and communities is often devastating, and the economic burden on society can be substantial. Suicide by ingesting pesticides is estimated to account for about one third of all suicides worldwide and is a problem particularly in rural agricultural areas in South-East Asia, Africa, and the Western Pacific (WHO 2014). The WHO concluded that restricting access to pesticides is an effective strategy for preventing suicides. In the Caribbean paraquat caused most fatal poisonings due to poor regulatory control (Pinto Pereira et al 2007).

Easy access to toxic pesticides is an important factor contributing to high numbers of deaths caused by suicidal ingestion of a pesticide. Several studies found that suicides were more numerous in agricultural areas and during the farming season. It has been argued that a ban or severe restriction of acutely toxic pesticides would have a limited impact as vulnerable individuals could choose another poison. However in several countries banning highly toxic pesticides has proven an effective way to reduce the number of deaths from self-. Recent data on self-harm with pesticides from Sri Lanka confirmed earlier findings that regulations restricting the availability of potentially lethal pesticides, and paraquat in particular, have been successful as suicide numbers have dropped, while the extent of substitution with other lethal methods was limited (Knipe et al 2015 & 2014; Pearson et al 2014), This was also found in South Korea (Lee et al 2015; Myung et al 2015) where a study conducted before paraquat had been banned (in 2011/12) found that nearly two thirds of survivors who had attempted suicide by ingesting paraquat had not known about its particularly hazardous properties (Seok et al 2009). Earlier studies in Taiwan also found that restrictions on pesticides resulted in fewer deaths by suicide without substitution of method (Lin & Lu 2011). In India, four village communities that stopped pesticide use in favour of non-chemical alternatives observed fewer suicides afterwards (Vijayakumar & Satheesh-Babu 2009).

Although product formulations with a lower percentage of the paraquat active ingredients have been made available, these are not always successful in preventing deaths following self-harm. In Japan no reduction in the mortality rate of paraquat poisonings due to self-harm was achieved after introduction of a formulation containing only 5 % of paraquat. Additionally, trends in the number of fatal suicides with paraquat and the amount sold in Japan appear correlated (Nagami et al 2013). For a mixed product – containing 5 % paraquat plus 7 % diquat – the mortality rate was 79.2 % and even higher than the rate of 71.4 % for 24 % paraquat (Ichinose et al 2004). It is worth noting that, suicide or self-harm can be over-represented in national statistics compared to occupational poisonings. Self-harm cases are more severe and medical intervention is more likely to be sought. Self-poisoning cases thus are more likely appear in a countries' national poisoning statistics, while occupational cases are often under-reported (see Corriols Molina 2009).

3.2 – GLOBAL PREVALENCE

WHO 2014 – Preventing suicides and self harm[139]

Most suicides in the world occur in the South-East Asia Region (39 % of those in low- and middle-income countries in South-East Asia alone) with India accounting for the highest estimated number of suicides overall in 2012. Comparing estimates for 2000 with those for 2012, there was an increase of 38 % in suicide rates in the African Region. Suicide by intentional pesticide ingestion is among the most common methods of suicide worldwide, particularly in rural agricultural areas in South-East Asia, Africa, and the Western Pacific.

"Restricting access to the means for suicide works. An effective strategy for preventing suicides and suicide attempts is to restrict access to the most common means, including pesticides, firearms and certain medications. [...] Access to the means of suicide is a major risk factor for suicide. [...] in 2012 the South-East Asia Region accounted for 26 % of the global population but for 39 % of global suicides. [...] Pesticides account for an estimated one third of the world's suicides (Gunnell et al 2007a). Suicide by intentional pesticide ingestion primarily occurs in rural areas of low- and middle-income countries in Africa, Central America, South-East Asia and the Western Pacific. Measures proposed to prevent suicide by pesticides include: ratifying, implementing and enforcing relevant international conventions on hazardous chemicals and wastes; legislating to remove locally problematic pesticides from agricultural practice; enforcing regulations on the sale of pesticides; reducing access to pesticides through safer storage and disposal by individuals or communities; and reducing the toxicity of pesticides (Eddleston et al 2001; Gunnell et al 2007b). [...] Restriction of access to means plays an important role in suicide prevention, particularly in the case of suicides that are impulsive. Implementation of effective policies coupled with community interventions has been instrumental in reducing suicide through means restriction." [pp. 11, 18, 33, 71]

WHO 2009 – Banning and restricting highly hazardous pesticides reduces mortality from suicide[140]

"Safer storage, bans and replacement by less toxic pesticides could prevent many of the estimated 370 000 suicides caused by ingestion of pesticides every year. Members of agricultural communities in low- and middle-income countries are heavily over-represented in the suicide death toll related to pesticides. Controlling access to pesticides is not only critical in reducing self-directed violence, it is key to preventing unintentional poisoning and terrorism. International conventions attempt to manage hazardous substances; however, many highly toxic pesticides are still widely used. Studies indicate that bans must be accompanied by evaluations of agricultural needs and replacement with low-risk alternatives for pest control." [p. 3]

Pesticides: facts and figures (WHO 2009)

- Pesticide ingestion accounts for an estimated 370 000 suicides each year, worldwide, more than one third of all suicides (Gunnell et al 2007).
- The proportion of suicides by ingestion of pesticides varies from 4 % in WHO's European Region to 56 % in its Western Pacific Region (Gunnell et al 2007). A disproportionate number of suicides by pesticide self-poisoning occur in low- and middle-income countries.
- In many rural areas of South-East Asia, pesticide ingestion accounts for over 60 % of suicides (Gunnell et al 2003). Estimates suggest that more than 160 000 people in this region kill themselves each year by ingesting pesticides (Gunnell et al 2007).
- The toxicity of pesticides to humans varies widely; ingestion of paraquat is fatal in over 60 % of self-poisoning cases (Wilks et al 2008), compared with less than 10 % for the insecticide chlorpyrifos (Eddleston et al 2005).
- Pesticide poisoning places huge burdens on health services in developing countries. [...] The overall estimated cost of treating self-poisoning cases in Sri Lanka in 2004 was about $1 million (Wickramasinghe et al 2009).

Legislative measures: "Policies that restrict or ban the use of highly toxic substances can reduce access to lethal means and reduce suicide mortalities. Evidence of the impact of such bans on suicide mortality is available from several countries. [...] In Samoa, a rapid increase in self-poisoning and suicide occurred following the introduction of paraquat in 1974. Reduced imports of paraquat from 1982 onwards – rather than a legislative ban – resulted in a subsequent drop in suicide rates (Eddleson et al 2002)."

WHO (2008). Clinical management of acute pesticide intoxication: Prevention of suicidal behaviours

www.who.int/mental_health/publications/9789241596732/en/

"Other classes of pesticide [besides organophosphates (OP)] that are common causes of significant and/or fatal poisoning include carbamate and organochlorine insecticides, the fumigant aluminium phosphide (a significant problem in north India), and the herbicide paraquat. [...] The case fatality for different pesticides also varies markedly, from around 70 % for both aluminium phosphide and paraquat, to close to 0 % for many of the newer lower toxicity pesticides (Dawson and Buckley, 2007; Eddleston, 2000). [...] More than half of global deaths from pesticide poisoning occur in China (Buckley et al, 2004; Phillips et al, 2002) [...]

3.3 – AFRICA

TANZANIA

Lekei et al 2014, 2012 – Pesticide poisoning impacts significantly on communities; surveillance needed[141]

Admissions of patients to 30 hospitals and health care facilities due to acute pesticide poisoning in Tanzania between 2001 and 2005 were examined (restrospective study). Of these health facilities, 22 reported one or more cases of pesticide poisoning. In total, 656 cases were reported in retrospection for the five-year period. A follow-up (prospective) study in 2006 over 12 months focused on 10 facilities with the highest reporting of pesticide poisonings: 230 cases. Most poisoning agents identified were pesticides in WHO class I and II. Contrasting retrospective and prospective studies, annual incidence rate almost tripled and mortality rate doubled in 2006, compared to the five preceding years. Case fatality decreased from 7.8 % (retrospective) to 5.6 %

in the prospective study. Missing data on circumstances and agents decreased from 24.1 % (2001–2005) to 9.9 % (in 2006). Despite this improvement, reporting could not generate all information required for the notification of banned or severely restricted chemicals under the UN's PIC Convention.

Of the pesticide poisonings with known circumstances, occupational cases were less common (c. 5 %), while self-harm/suicide (27.8 %), accidental cases (26.4 %) and unknown circumstances (41.0 %) were more frequent from 2001 to 2005. In 2006, the proportion of self-harm cases was higher (47.0 %), followed by accidents (25.3 %), cases with unknown circumstances (18.7 %), and occupational cases (8.3 %).

Fatalities were usually associated with self-harm. Most poisoning victims were reported to have recovered, while two were left with a permanent disability. The study is likely to have underestimated patients with less severe poisoning who required no medical treatment. In over half (probably over 2/3) of poisoning cases the responsible pesticides were not identified. Between 2001 and 2005 only 17 % of causal agents were specified, and 23 % in 2006; organophosphates comprised ca. 60 %, followed by zinc phosphide, pyrethroid and organo-chlorine insecticides, sulphur, carbamates, paraquat and other pesticides. Paraquat was reported in 2006 and during 2001–2005. In 2006, 'other agents' – paraquat, organometals, amitraz, glyphosate, and chlorothalonil – accounted for 30 of 230 poisonings (13 %), and paraquat was implicated in about 4 % of cases.

The strong increase in reporting in 2006 may be due to greater awareness of the need to record poisonings. This indicates that usually (without external surveillance) about 2/3 of patients admitted to health facilities for pesticide are not reported. The higher incidence rate in 2006 (4.05 per 100'000) is much lower than in many other parts of the world. This might result from a true difference or from underreporting. Self-harm cases are much more likely to be fatal, therefore they often receive higher priority and better reporting than occupational or accidental cases. An earlier study in South Africa found that the occupational poisonings were hugely underreported (about 10-fold) compared to suicides (London et al 1997). The finding that women's risk for poisoning increased in the prospective study indicates some underreporting. Lacking data on specific poisoning agents is of great concern for prevention and for reporting within the UN's Prior Informed Consent ('Rotterdam') Convention which signals that a pesticide presents a hazard under "normal" conditions of use.

In another study Lekei et al (2014) 142 found that pesticide sellers in Tanzania contributed to an increased risk among the end-users. Unsafe practices of retailers include repackaging of product, spillage, unsafe disposal of empty containers, selling unauthorized products. Some product labels for paraquat were substandard.

3.4 – ASIA

CHINA

Wong et al 2006 – Death from accidentally ingesting one sip of paraquat solution; very high mortality[143]

"Seven cases of paraquat poisoning were treated in Tuen Mun Hospital [in Hong Kong] from 1998 to 2005. The mortality (4 out of 7) was very high. [...] Five of the cases (1, 2, 4, 5 & 7) had paraquat solution ingested for suicidal attempt. Three cases (1, 5 & 7) had exposure to large amounts (100 ml to 500 ml). These three patients developed pulmonary complications and acute renal failure (ARF), and subsequently died. Case 5 who ingested a large amount of paraquat solution (200 ml) died even after immunosuppressive and anti-oxidant therapies were tried. She had severe complications. [...] The patient in case 3 accidentally ingested one mouthful of paraquat solution and attended the accident & emergency department (AED) three days after the exposure. He presented with generalised malaise and developed ARF [acute renal failure] [...] After two courses of haemodialysis [...] He was also given steroid therapy. However, he died subsequently [18 days later] with progressive pulmonary fibrosis and type 1 respiratory failure [...] after only a sip of paraquat solu-tion. Two patients with oral exposure to paraquat survived and the amount of paraquat involved in both cases were small (case 2 & 4). The patient in case 2 drank 20 to 40 ml paraquat solution for suicidal attempt [...] Case 4 was a young man who attempted suicide by drinking half-spoonful of paraquat solution. He was given activated charcoal in the AED and Fuller's earth after admission. Steroid therapy was also given. He developed ARF [...] even with charcoal haemoperfusion performed soon after admission. His renal function gradually improved to normal in one week's time with supportive haemodialysis. He did not develop pul-monary complication clinically all along but no lung function test was done. He was subsequently discharged 23 days after admission. One case of ocular exposure to paraquat survived and the patient was free from systemic complications during the hospital stay (case 6). [...] There were no qualitative or quantitative laboratory tests, such as urine dithionite test and serum paraquat assay, performed in all the seven cases." [pp. 155-7]

INDIA

Harshavardhan et al 2014 – Increasing numbers of suicidal paraquat poisonings in Karnataka[144]

"This is a retrospective study of patients admitted to the General medicine department of Hassan Institute of Medical sciences, Hassan, Karnataka [India], between March 2012 to March 2013 for alleged paraquat poisoning. [...] Out of 77 patients presented with acute paraquat poisoning, there were 2.2 times more males and about half of them were in third and fourth decade. Suicidal exposure was the single most important reason for exposure which is accounting for 91 %. Most of the patients (52 %) consumed more than the lethal dose of the poison i.e, > 40 ml. Many patients reported after critical time of > 6 hours [...] Patients with unknown outcomes (n = 17) who made their own decision to be discharged from the hospital were excluded from further analysis. Among the remaining cases (n = 60), 21 poisoning-related fatalities were reported, and these were predominantly male patients (61 %). [...] Because a high proportion of Indian population is involved in agriculture, the incidence of suicidal PQ [paraquat] poisoning is increasing as a result of easy access to highly toxic weedicides in the situations of stress. [...] Paraquat is one of the most widely used weedicides globally and in most countries it is used without restrictions. However, some

Smallholder farmer spraying paraquat (Pakistan) | © Marion Nitsch

countries have restricted its use. Relatively few exposure studies and hardly any intervention studies have been performed. This study concludes that, paraquat is a widely used weedicide by the farmers in the rural areas in and around the Hassan, suicidal ingestion is more common than occupational exposure in contrast to developed countries. Patient who has taken < 20 ml and reported < 6 hours shown better recovery in compared to their counter parts." [pp. 3577-79]

Hemachandar R. 2014 – Paraquat poisoning common in India but rarely reported[145]

A 34-year old woman who had ingested paraquat three days earlier was referred to a hospital in Puducherry, India. Despite immunosuppressive treatment she died from respiratory failure after three more days. Paraquat is not removed by dialysis which is usually only applied in poisoning cases with acute kidney injury (Wong et al 2006). Mortality of paraquat poisoning remains high even with prompt management.

"The diagnosis in our patient was based on the history and direct verification of the container containing paraquat. Urinary examination for paraquat could not be done due to non availability. [...] To conclude, *paraquat poisoning has become a common entity in India, yet it is rarely reported and is associated with a high mortality rate.* There is no specific antidote available for paraquat poisoning. Early diagnosis and aggressive decontamination is pivotal. The role for immunosuppressive therapy in patients with paraquat poisoning is not clear due to paucity of clinical trials in this area." [p. 49]

Kanchan et al 2015 – Paraquat causing high proportion of fatal poisonings in tertiary hospital, south India[146]

"The present research constituted of a series of 14 cases of fatal paraquat poisoning during 2009–2010 [...]. Paraquat poisonings constituted 14.4 % of the total poisoning fatalities during the study period. [...] In the present series paraquat was ingested in all the cases with suicidal intent reported in all but one case. Till date there is no single accepted guideline for treatment of paraquat poisoning. [...] It is recommended that the availability of this highly toxic substance be restricted so as to prevent its misuse as a method of suicide."

Peranantham et al 2015 – Strict regulatory measures needed for pesticide sales[147]

A man who was hospitalized in Puducherry for diazepam and paraquat poisoning died on the following day.

"In India, most of the concentrates of paraquat are available as 10-20 % solutions. [...] Paraquat poisoning has high mortality even in small quantity due to multi organ dysfunction syndrome. Surveillance of misuse should be undertaken in the current use. [...] consumers, family members, and others should be aware of the associated risk these substances pose. [...] Strict legislation measures must be imposed by the government regarding the sales of herbicides and pesticides." [pp. 98, 100]

Raghu et al 2013 – Paraquat poisoning: poor prognosis and high mortality[148]

"Although it is uncommon, paraquat ingestion can lead to severe and often fatal toxicity.[6-8] However, although it is widely available, reports of this herbicide poisoning are not common in India.[9-13] We discuss a fatal case of suicide in which paraquat was consumed [...] In spite of advances in medical care, prompt treatment, and supportive care, mortality is high (mainly due to multiorgan system and respiratory failure) in patients with paraquat poisoning. [...] Although there have been isolated case reports of survivors (mainly due to the smallness of the dose or effective and early treatment) [Sandhu 2003], an ingestion of a high dose or severe paraquat poisoning has a poor prognosis. At present, there is no specific antidote to paraquat poisoning. Therefore, it is recommended that the crucial focus should be on preventive measures and in case of exposure, when it has been ingested, the institution of aggressive decontamination to prevent further absorption."

Ravi Kumar & Punitha 2013 – Paraquat most often used pesticide causing death due to self harm[149]

"Paraquat is considered the most poisonous herbicide in wide use. Paraquat is freely available in the Indian market for agricultural use. [...] The most frequent routes of exposure to Paraquat either accidentally or intentionally, in humans and animals are following ingestion or through direct skin contact (Khosya & Gothwal 2012) [...] Paraquat is the one of the most common pesticides causing death intentional self-poisoning, i.e. suicide. There is concern in developing countries that the easy availability of pesticides leads to suicides which might not otherwise occur. It has a 60-70 % mortality rate (Seok et al 2009), much higher than many other agents. Most cases are self-poisoning, but not all intend to die (Hettiarachchi & Kodithuwakku). This is very important, given that in countries such as developing nations intentional self-poisoning is "often a result of impulsive behaviour rather than the result of long-standing psychiatric problems". Sudden anger and grief are common triggers (Van der Hoek et al 1998). [...]

There are numerous designs, management, mechanical and cultivational practices, as well as some plant extracts, that can be used instead of Paraquat, depending on the weed species and the situation. By far the biggest cause of non-occupational poisonings is intentional self-poisoning, i.e. suicide. This problem is central to the problem of Paraquat: if Paraquat were banned worldwide and so no longer available, many thousands of lives would be saved, whether from occupational poisoning, suicide, or accidents to children. All other herbicides on the market have lower acute toxicity than Paraquat." [pp. 3-4]

Shashibhushan et al 2015 – Paraquat widely used; high mortality of paraquat poisoning (self harm)[150]

Paraquat is widely used in India and highly toxic. Mortality of paraquat poisoning is very high due to the lack of a specific antidote and effective treatment options. None of these worked in this case of a 30-year old man who had ingested paraquat 24 % concentrate. Three days later he was transferred from a local hospital to the emergency department at Bellary medical university, Karnataka. Liver function deteriorated and the patient developed renal failure and acute respiratory distress syndrome over the next few days. Different treatment strategies were attempted but none of these worked well and the patient died from multi-organ failure.

Vaishnavi 2011 – Poisoning case in Tamil Nadu; ban of paraquat considered necessary[151]

Case report: A 17-year old woman had ingested 10 ml of paraquat intending self-harm. After four days she was referred from a regional hospital to the Sri Ramachandra Medical University in Chennai, Tamil Nadu, due to kidney failure and liver dysfunction. She underwent hemodialysis and was given supportive and antibiotic treatment. She later developed progressive respiratory distress, requiring intubation and ventilation, and she received immune-suppressive treatment. Due to financial constraints she left hospital ten days later 'against medical advice' (AMA). The author concluded: "Paraquat needs to be banned in India also." [p. 32]

JAPAN

Nagami et al 2013 – Less concentrated paraquat products do not achieve decrease in mortality rate[152]

"Japan is one of the few countries that has experience in distributing and using 5 % products of Pq [paraquat], a herbicide. The authors studied Pq poisoning cases of attempted suicide on the basis of surveys performed on clinical cases of pesticide poisoning by JARM-affiliated hospitals. The mortality rate for suicide attempts with Pq products is somewhere around 80 % even for 5 % products, so the attempts to decrease the mortality rate with Pq products having lower concentration did not prove to be effective. It has also been suggested that trends in the number of deaths from suicidal attempts with Pq and the amount of Pq shipped are correlated.

A wide variety of therapies have been studied in the last several decades, to be sure, but few therapies have been developed to decrease the mortality rate in an effective manner. As efficacious therapies for Pq poisoning remain elusive, Pq should at least be categorized into Class Ib (highly hazardous)." [pp. 231-232]

Nagami 2010 – Ban of paraquat demanded in Japan 30 years ago; diluted product equally dangerous[153]

"In Japan, attention was focused on paraquat, a non-selective herbicide, as a pesticide that could cause many deaths. At the 34th Congress of the Japanese Association of Rural Medicine, where Wakatsuki served as president, a resolution was adopted against the spraying of paraquat (JARM 1985). As the JARM membership consisted mainly of medical workers assigned to hospitals under the umbrella of the National Federation of Agricultural Cooperatives for Health and Welfare, a series of heated arguments developed between them and the pesticide users. After the discussions, the JARM released a statement (1) suggesting that paraquat should be classified as a specific poisonous substance and (2) that there should be ongoing, thorough guidance on protective gear to be utilized when using paraquat. In the face of this declaration, the makers of paraquat reduced the concentration from 25 % to 5 % in 1986. As deaths continued to occur after that, Ichinose et al.[31] and Nagami et al.[27] reported that the reduced concentration did not effectively drop the rate of deaths from suicide poisoning. Moreover, Nagami et al.[27] argued there was the need for stricter control of distribution because the curves proposed by Proudfoot et al. in 1979 for distinction between life and death remained valid even though 30 years had since elapsed and a therapy for prevention of death from shock or multi-organ insufficiency had yet to be worked out."

SOUTH KOREA

Cha, Chang, Eddleston et al 2015 – Impact of paraquat regulation on suicide in South Korea[154]

"Pesticide suicide mortality halved from 5.26 to 2.67 per 100'000 population between 2011 and 2013. [...] The absolute reduction in the number of suicides was greatest among men, the elderly and in rural areas. The reduction in pesticide suicides contributed to 56 % of the decline in overall suicides that occurred between 2011 and 2013. There was no impact of the regulations on crop yield. [...]

Conclusions: The regulation of paraquat in South Korea in 2011–12 was associated with a reduction in pesticide suicide. Further legislative interventions to prevent the easy availability of highly lethal suicide methods are recommended for reducing the number of suicides worldwide.

Key messages:
- Restricting access to toxic pesticides can reduce the suicide rate from pesticides and from all methods.
- The absolute reduction in pesticide suicide mortality rates following bans on the sale of paraquat in South Korea was greatest among men, the elderly, and people living in rural areas.
- In countries where pesticides are commonly used as a method of suicide, legislative bans on the most toxic products are likely to reduce overall suicide rates."

Cha, Khang et al 2014 – Delayed impact of restrictions on availability of paraquat in South Korea[155]

"Suicide through pesticides is the second-most frequently used method, which accounted for 20.8 % of total suicides, followed by hanging (50.9 %) in South Korea during the study period of 2006 through 2010. [...] The high rate of pesticide ingestion in suicide in South Korea may be explained by their easy accessibility

[...] The regional and seasonal variations in pesticide poisoning presented in this study may also corroborate this explanation of accessibility to pesticides. Considering that widespread access to pesticides may easily convert a number of impulsive acts into suicide by means of pesticide ingestion, restrictions on pesticides should be a priority for suicide prevention efforts in South Korea. The study results showed that pesticide self-poisoning is a largely rural phenomenon and is the most common method of self-harm resulting in death, accounting for 47.4 % of total rural suicides in South Korea. [...] Although South Korea implemented the Act on Paraquat Regulations in 1999 and revised it in 2005, mortality due to paraquat was still seen to be high thereafter. Recently, the South Korean government banned the selling of paraquat from the end of 2012 but the paraquat sold prior to the ban continues to exist in South Korea due to the lack of further progressive policies such as recalling para-

quat from the market and from farmers. [...] The majority of pesticide poisoning deaths were the result of intentional poisoning; in particular, elderly suicide by pesticide ingestion in rural areas was shown to be a serious social problem. Easy access to pesticides and the lack of management of suicide by pesticide ingestion in rural area are suggested as major factors related with the high rate of pesticide poisoning in South Korea. Therefore, intensive intervention efforts, such as the strict regulation of toxic pesticides and prevention efforts directed at controlling suicide are critically needed to reduce the burden of pesticide poisoning in South Korea." [p. 4, p. 7]

Choi, Kim et al 2012 – Economic burden of pesticide poisoning in South Korea largely unnoticed[156]

In South Korea acute pesticide poisonings (APP) are very numerous, with an estimated incidence in 2009 of 23.1 per 100 000 population and a mortality rate of 2.6 per 100 000. Besides the personal tragedies of so many lost lives, these premature deaths result in an enormous economic burden to society. However indirect costs, the major part, remain hidden and are neglected. Based on data of the National Health Insurance (NHI), a total of 11 453 patients were treated for APP in 2009. Half of these were hospitalized, and 1311 patients died, resulting in a case fatality rate of 11.4 %. Total costs of APP in 2009 were estimated at approximately US$ 150 million. Of this amount, 90 % originated from the indirect costs due to premature mortality.

The authors of this study concluded: "The substantial proportion of indirect costs can be mainly attributed to the high case fatality rate of APP in South Korea. Because intentional self-poisoning accounted for 84.8 % of total deaths from pesticide poisoning in South Korea (Lee et al. 2009), the large proportion of mortality cost should be closely linked to suicide. The case fatality rate of 11.4 % in this study is comparable to that of emergency room visit patients of 15.0 % (Ko et al. 2012) and that of hospitalised patients of 19.1 % (Kim et al. 2012), considering that NHI data included ambulatory and/or non-emergency cases as well. This high fatality may result from the possible exclusion of mild cases, which did not receive medical attention because NHI data do not capture such cases. The high proportion of self-poisoning from paraquat and the advanced age of the victims may also partially explain the reason."

It follows for the study's authors that regulations need to be reinforced to reduce pesticide poisonings as the wide availability of pesticides was found also in other studies to be one of the most important risk factors for suicide by self-poisoning. They consider a ban of highly lethal pesticides offers an urgent and effective tool to reduce the number of deaths from pesticide poisoning in the South Korean context of a high suicide rate and inadequate current pesticide regulations. Many industrialised countries have banned a number of highly toxic pesticides such as paraquat, and in South Korea this was banned in 2012. The authors noted that there may be a degree of under-reporting of occupational pesticide poisoning cases, leading to an underestimation of poisoning incidence and ensuing costs. The study did not account for disability costs and the impact of suicide on the community, therefore it underestimates the burden of pesticide poisoning on society. [pp. 1538-42]

Jang, Kim et al 2013 – Acute poisonings in South Korea 2003 and 2011, before and after paraquat ban[157]

Medical records on 939 patients treated for acute poisoning at emergency departments of three South Korean hospitals between 2003 and 2011 were analyzed. Suicide was the most common cause and this did not change over time. Among the patients who died from acute poisoning in the first and last year of the period studied, paraquat was the most frequent causal agent. Paraquat poisoning was responsible for 5 of the 6 deaths in 2003 and 5 of the 9 deaths in 2011. In South Korea, the sale and production of paraquat are forbidden by law since 2012. Accordingly, a decrease in mortality due to paraquat poisoning is expected.

Kang B. 2007 – Paraquat prominent cause of fatal poisonings in South Korea[158]

"The aim of this study was to investigate reports of toxicants on fatal toxicology research during the past two decades in Korea, with a focus on emergency symptoms. [...] The result suggest that over a 24-year-period, carbon monoxide, paraquat, and organophosphate pesticides have been prominent in both the incidence and severity of fatal toxic exposure in Korea, which underscore the need for review of them."

Lee & Cha 2009 – Paraquat main cause of pesticide poisoning in South Korea, especially in farming season[159]

"During the period of 1996–2005, an approximate average of twenty-five hundred fatalities occurred per year due to pesticide poisoning, while age-standardized mortality rates by pesticide poisoning significantly increased from 4.42 to 6.42 per 100,000 population. Intentional self-poisoning was the primary cause of death due to pesticides (84.8 % of total pesticide poisoning deaths). The prevalence of non-fatal pesticide poisoning among farmers varied from 5.7 % to 86.7 %. Paraquat was the leading causative agent for pesticide poisoning, followed by organophosphate insecticides. A variety of work-related factors such as pesticide usage, pesticide application days, hazardous practices and poor personal hygiene were significantly related with pesticide poisoning. The majority of the poisoned were male, elderly individuals possessing low levels of education and residing in rural areas. The number of pesticide poisoning cases was the highest during the growing season of May to August."

Lee, Hwang et al 2015 – Marked decrease in number of suicides after paraquat ban in South Korea[160]

"The total number of suicide attempts decreased from 399 in 2011 to 245 in 2014 [...] The ratio of persons completing suicide to those attempting suicide after pesticide ingestion has decreased every year after the PQ ban. [...] Among herbicides, the majority (40.2 %) of patients ingested PQ paraquat]. [...] Until the 2012 ban in Korea, PQ was the most commonly used pesticide for suicide attempts, with an estimated 2,000 toxic ingestions annually and 60 %-70 % mortality. [...] our study shows that the number of suicide attempts and the proportion of PQ to pesticides decreased significantly after the PQ ban. Furthermore, the decreasing proportion of PQ to all herbicide categories increased annually. There was a significant increase in the annual number of suicides and the proportion using glyphosate

and glufosinate. However, the number of suicide attempts using glyphosate and glufosinate is not as high as PQ." [pp. 1518-20]

Myung et al 2015 – Paraquat prohibition and change in the suicide rate and methods in South Korea[161]

"The annual suicide rate in South Korea is the highest among the developed countries. Paraquat is a highly lethal herbicide, commonly used in South Korea as a means for suicide. We have studied the effect of the 2011 paraquat prohibition on the national suicide rate and method of suicide in South Korea. We obtained the monthly suicide rate from 2005 to 2013 in South Korea. In our analyses, we adjusted for the effects of celebrity suicides, and economic, meteorological, and seasonal factors on suicide rate. We employed change point analysis to determine the effect of paraquat prohibition on suicide rate over time, and the results were verified by structural change analysis, an alternative statistical method. After the paraquat prohibition period in South Korea, there was a significant reduction in the total suicide rate and suicide rate by poisoning with herbicides or fungicides in all age groups and in both genders. The estimated suicide rates during this period decreased by 10.0 % and 46.1 % for total suicides and suicides by poisoning of herbicides or fungicides, respectively. In addition, method substitution effect of paraquat prohibition was found in suicide by poisoning by carbon monoxide, which did not exceed the reduction in the suicide rate of poisoning with herbicides or fungicides. In South Korea, paraquat prohibition led to a lower rate of suicide by paraquat poisoning, as well as a reduction in the overall suicide rate. Paraquat prohibition should be considered as a national suicide prevention strategy in developing and developed countries alongside careful observation for method substitution effects."

Seok et al 2009 – Survivors of attempted suicide in South Korea: only a minority chose paraquat knowingly[162]

"This study analyzed 250 cases (143 males, 107 females) of attempted suicide with PQ ingestion. The patients were admitted to the Institute of Pesticide Poisoning (IPP), Soonchunhyang University Cheonan Hospital, from January through December 2007. We evaluated their medical records retrospectively to determine the reasons for the use of PQ. Additionally, we assessed how the PQ was obtained. Patients were included if they had a positive PQ urine test and completed a questionnaire. [...] The intentional selection group was defined by the answer to the question, "Did you select PQ after considering other pesticides?" Additionally, the means of obtaining the PQ was divided into two categories: purchased (situations in which patients bought a new bottle of PQ) and preexisting (wherein patients already had PQ available).

In 2007, 469 patients who attempted suicide after swallowing a pesticide were admitted to our hospital (unpublished data); PQ accounted for 301 (64.2 %) of those cases. The 250 cases reported here is the largest one-years experience reported by any hospital, to our knowledge. [...] We sorted the patients into two groups, the intentional and non-intentional selection groups, to determine whether the patients had specific information about PQ, such the lack of an effective therapy and the consequent high mortality rate. The intentional selection group accounted for 38.4 % of cases. This result suggests that almost two of every three patients ingested PQ simply because it was available when they attempted suicide. Some of the patients bought an herbicide from a shop without mention of a specific trade name and it simply turned out to be PQ. [...] In conclusion, only 38 % of the patients who attempted suicide with PQ actually intentionally chose PQ. Thus, it is important to decrease the accessibility of PQ to improve suicide prevention. In particular, control of the storage of pesticides on farms and control of the purchase of pesticides by farmers would be helpful." [p. 248, p. 251]

SRI LANKA

Eddleston et al 2012 – Effects of provincial pesticide ban on hospital admissions for pesticide poisoning[163]

This study mentions paraquat in the context of the success of its ban in Sri Lanka to argue for bans on other pesticides causing incidents of poisoning. Pesticide self-poisoning causes about one third of global suicides. Sri Lanka halved its suicide rate by banning WHO Class I organophosphorus [OP] insecticides and then endo-sulfan. But poisoning with WHO Class II pesticides including paraquat remains a problem. The authors aimed to determine the effect and feasibility of a ban of the two insecticides in one Sri Lankan district. The case fatality of paraquat (42.7 %) was much higher than that of two OPs and it still kills many people every year.

„[...] two highly toxic OP insecticides were selected for the study. However, the herbicide paraquat was an important cause of death throughout the period of this study. [...] The importance of paraquat as a cause of fatal self-poisoning was not well recognised at the time that the study was designed and started22; as a result, the hoped for effect on overall pesticide deaths by banning two insecticides was obscured." [p. 208]

Conclusions: The study found that the OP insecticides could be effectively banned from agricultural practice, as shown by the fall in hospital admissions, with few negative consequences. However, the ban of two OPs had only a minor effect on pesticide poisoning deaths because it was too narrow.

Knipe et al 2014– Regulation of toxic pesticides results in reduced suicide numbers over past decade[164]

"[...] a series of company trials and further regulations, starting in 2004 and culminating in 2008, have occurred in Sri Lanka, these resulted in reductions in the toxicity of highly toxic paraquat formulations. These interventions were followed by a complete ban on paraquat, dimethoate, and fenthion, from 2011."

"The epidemiology of suicide in Sri Lanka has changed noticeably in the last 30 years. The introduction of pesticide regulations in Sri Lanka coincides with a reduction in suicide rates, with evidence of limited method substitution."

Pearson, Zwi et al 2014; 2015 – Withdrawal of paraquat from the market in 2008 has reduced mortality[165]

"This review aimed to systematically appraise what is known about suicide in Sri Lanka. [...] there remains limited evidence of prevention, risk factors, health services, and policy. A wide

range of solutions have been proposed, but only regulation of pesticides and improved medical management proved to be effective to date."

"In 2008, the Department of Agriculture [DoA] announced a phased withdrawal of three more pesticides (paraquat, dimethoate and fenthion) based on strong evidence of the high case fatality associated with their misuse in rural communities [...] a National Policy and Action Plan on Prevention of Suicide released in 1998 [...] This also signalled an important shift within the DoA in relation to how it viewed suicide; it had previously been viewed as a social problem beyond their remit. However, links between health and agriculture connected the problem to the easy availability of pesticides and specifically to their sales, marketing and promotion. [...]

The regulation of pesticides in Sri Lanka over a period of 20 years has reduced the mortality from suicide; policymakers in agriculture responded to a perceived crisis." [Pearson et al 2015; pp. 58, 61, 63, 65]

TAIWAN

Lin, Chang & Lu 2010 – Paraquat most frequently used pesticide to self harm in Taiwan[166]

"Of 1651 suicides by pesticides occurred between 2006 and 2008, 541 (32.8 %) cases used herbicides, 306 (18.5 %) cases used insecticides, 38 (2.3 %) cases used other pesticides, and 766 (46.4 %) cases did not report specified type of pesticides. Paraquat was the most common used herbicides (471 cases) and organophosphates (130 cases) and methomyl (97 cases) were the two most often used insecticides in Taiwan." [p. 3]

Chang, Lu et al 2012 – Suicide by pesticide poisoning in Taiwan: analysis of trends 1987–2010 and factors[167]

Pesticide poisoning was the most commonly used method of suicide in 1987 but had become the third most common method by 2010. The reduction was paralleled by a 66 % fall in the workforce involved in agriculture but there was no strong evidence for its association with trends in pesticide sales, bans on selected pesticide products or unemployment. The bans mostly post-dated the decline in pesticide suicides; furthermore, they did not include products (e.g. paraquat) that accounted for most deaths and were mainly restricted to selected high-strength formulated products whilst their equivalent low-strength products were not banned.

Conclusions. Access to pesticides, indicated by the size of agricultural workforce, appears to influence trends in pesticide suicide in Taiwan. Targeted bans on pesticides should focus on those products that account for most deaths.

3.5 – EUROPE

Cassidy et al 2014 – Fatal poisonings reported in Ireland from 2000 to 2012: 21 % of cases due to paraquat[168]

"Over the 13-year study period [2000 to 2013], the NPIC was consulted about 151 suspected poisoning cases that subsequently had a fatal outcome. [...] The principal agents implicated in fatal cases were pharmaceuticals (n = 75, 49.67 %), agrochemicals (n = 36, 23.84 %), drugs of abuse (n = 20, 13.25 %), industrial agents (n = 9, 5.96 %), unknown agents (n = 7, 4.63 %), household products (n = 3, 1.99 %) and 1 cosmetic agent (0.66 %). Paraquat poisoning was implicated in 21.19 % (n = 32) of fatalities." [p. 309]

De Groot et al 2015 – Obsolete stocks of paraquat still accessible in Europe ten years after ban[169]

A fatal case of paraquat poisoning in the Netherlands in 2014 is described. This was due to deliberate ingestion.

Ferrer-Dufol et al 2014 – Fatal poisonings in Spain, 1999 to 2014: Less cases due to paraquat since ban[170]

"Main chemical substances currently producing acute poisoning are: toxic gases (systemic and irritants), liquid caustics, solvents, pesticides, and detergents. [...] There were 127 registered fatal cases [between 1999 and 2104], giving a mortality rate of 1.47 % which is higher than the mortality rates of the total acute poisonings which is less than 0.5 % in Spanish hospitals. [...] The type of poisoning was a suicide gesture in 87 cases (69 %), domestic accidents in 28 cases (22 %) and occupational accidents in 6 cases (5 %). The mortality rate by chemical family was: pesticides 5.0 %, caustics 2.0 %, solvents 1.9 % and toxic gases 0.8 %. The mortality rates for the more dangerous agents were: carbon monoxide (CO) 0.86 %, methanol 14.88 %, hydrochloric acid (HCl) 20.22 % and paraquat 44.20 %. Only three paraquat cases, with one lethal, have been registered since the EU banning of this herbicide in 2007. [...] Lethal cases are more common in the older population and are mainly due to suicidal gestures. The most dangerous agents are paraquat, HCl, methanol, and CO. The EU regulation on paraquat has proved to be effective in preventing these most dangerous poisonings." [p. 310]

Kastanaki et al 2010 – Suicide by pesticide poisoning, findings from the island of Crete, Greece[171]

Pesticide use in Greece rose by 39 % over the period 1990–1992 to 2002–2004. This study investigated the epidemiology of pesticide suicide on the Greek island of Crete, a largely rural agricultural area. The study explored victim profiles, as well as patterns and trends of pesticide ingestion, to suggest probable preventive measures. Self-poisoning suicides between 1999 and 2007 were reviewed and information gathered was entered into a computerized database. The overall incidence of intentional pesticide poisoning was 1.7 per 100,000, accounting for a quarter of the suicides in Crete. Paraquat and methomyl were the main pesticides ingested. The victims were largely middle aged male, rural habitant. More detailed research is required to identify aspects of these deaths amenable to prevention, but measures such as bans on the most toxic pesticides and changes in storage practice would appear to be sensible initial approaches.

Zilker T. 2012 – Poisoning over 50 years treated in toxicological center in Munich, Germany[172]

All cases treated in the years 1964, 1974, 1984, 1995, 2010 at the Toxicological Department of the Technical University, Munich were investigated.

Chemicals: carbon monoxide: 24 in 1964, still 19 in 2010. Lead (20) and paraquat (7) had a peak in 1974, organophosphates in 1984 (9).

Cause of death: paraquat 9/10 (90 %), parathion 5/15 (33.3 %), arsenic 2/18 (18.1 %), barbiturates 10/238 (4.2 %), carbromal 5/133 (3.8 %), TCA 4/154 (2.5 %), cocaine 2/115 (1.7 %), benzodiazepines 5/908 (0.55 %). Chemicals were always the number one killer.

Zoppellari, Fabbri, et al 2012 – Admissions to an intensive care unit following poisoning in Italy: 10-year study[173]

"Ten year (July 1 2001 – June 30 2011) prospective study including all patients admitted to our adult ICU [Intensive Care Unit, S. Anna hospital, Ferrara, Italy] with a main diagnosis of acute poisoning. We defined three criteria for ICU admission: the presence of vital function impairment (group 1); the perception that significant organ dysfunction could appear in asymptomatic patients on the basis of toxicokinetics or toxico-dynamics (group 2); a clinical judgment for intensive observation in mildly symptomatic patients (group 3).

Results: There were 107 poisoned patients (2.91 % of admitted patients) and 60.7 % were caused by miscellaneous agents. [...] Eight patients died: three after paraquat ingestion [...] Group 2 toxins were: paracetamol (3), acetonitrile (2), digoxin (2), paraquat (2) and ethylene glycol; only paraquat caused death."

3.6 – MIDDLE EAST

IRAN

Delirrad et al 2015 – Paraquat poisonings treated from 2007 to 2013 at Taleghani hospital of Urmia, Iran[174]

"In this cross sectional study, medical records of all paraquat intoxicated patients were reviewed at Taleghani hospital of Urmia, Iran, from 2007 to 2013 [...]. All [41] patients ingested the paraquat orally and other routes of poisoning were not observed. Ingestion of paraquat was for deliberate self-harm or suicide in 85.4 % (n=35), accidental in 9.8 % (n=4) and unknown in 4.9 % (n=2). The primary diagnosis was paraquat poisoning in 92.7 % (n=38), organophosphate poisoning in 4.8 % (n=2) and upper gastrointestinal bleeding in 2.4 % (n=1). [...] In our study, the majority of exposures (89.7 %) were intentional, mainly from deliberate self-harm. The previous study in Lorestan, Iran, by Amiri et al (2008) found that attempted suicide accounted for 76.9 % of poisonings25.

[...] Seasonal variation of paraquat poisoning is noticeable, more than 70 % of our cases occurred in spring or summer. This was similar to the study of Amiri et al [25] who reported more prevalence in the summer. Most of our cases were from north of the province, where farmers grow sunflowers in large quantities and use paraquat for eliminating weeds. Based on experts opinion in local office of Plant Protection Organization, the amount of paraquat used in one city (Khoy) are more than the total use of other cities in the province. Some studies suggest that the easy access to a potent substance, in this case paraquat, increases the number of suicides and may result in death when in fact there was no definite intention on the part of the victims to commit suicide [16]. Here, hemodialysis is used for the majority of our patients. Although, no significant relationship was found between hemodialysis and clinical outcome, overall in-hospital fatality in our center was 46.4 % which was less than very high case fatalities (50 %-90 %) reported in other studies [18, 26]. Whether our lower fatality rate associates with performing hemodialysis for the most cases, further investigation could show the effectiveness of hemodialysis on outcome of paraquat poisoning. The main limitation of our study was the inability to test the level of serum or urine paraquat. A semi-quantitative test using bicarbonate and sodium dithionite can be used as a bedside test to confirm systemic paraquat toxicity [...] Paraquat poisoning is still no cure. More research is needed to determine the effectiveness of various treatments. [...]"

Sabzghabaee et al 2010 – Fatality in paraquat poisoning, Iran[175]

A retrospective study in Isfahan, Iran, evaluated the cases of 29 patients suffering from acute following deliberate ingestion. Self-poisoning continues to be a major public health concern in many developing countries. This study was designed to compare the variables between survivors and non-survivors, these included: age and gender, the time from ingestion of paraquat to hospital admission, the amount ingested, occurrence of vomiting after ingestion, the time from hospital admission to initiation of haemodialysis, the length of hospital stay and the outcomes. The in-hospital fatality rate was 55.2 percent. No significant differences were observed between survivors and non-survivors with regard to patient characteristics. Most of the patients who died had ingested more than 40 mg/kg of 20 % paraquat (62.5 percent). A large amount of ingested paraquat, vomiting and age may be important variables to consider in association with the high fatality rate of poisoning. Current treatment in the hospital was unable to reduce fatality in paraquat poisoning cases. As such cases are common, there is an urgent need to develop preventive approaches.

3.7 – SOUTH AMERICA

CARIBBEAN

Pinto Pereira et al 2007 – Paraquat cause of most suicides in Trinidad and Tobago; poor regulatory control[176]

"Trinidad and Tobago, a twin-island republic, has the highest suicide rate among the Caribbean countries, and paraquat is responsible for most suicides (Hutchinson et al 1999). [...] Based on the number of retailers selling the item, pesticide sales were highest for paraquat, which was sold by 83 retailers (85.6 %). Gramoxone was reported as the most popular brand of paraquat by 80 retailers (82.5 %). [...] Over 50 % of retailers on the island reported that paraquat was sold most frequently [...] In the Caribbean, paraquat is most frequently used for poisoning by pesticide in Trinidad and Tobago (Hutchinson et al 1999) and Jamaica (Escoffery & Shirley 2004). In 1999, the incidence

of paraquat poisoning in Trinidad was 8 per 100 000 population (Hutchinson et al 1999). Of 105 fatalities following acute exposure in south Trinidad, paraquat was involved in 80 deaths and organo-phosphates in 10 (Daisley & Simmons 1999). Organophosphates and paraquat are also among the main causative agents of poisoning in Central America (Wesseling et al 2005). [...] Easy availability and ineffective regulatory control of pesticides make them a popular method of self-harm and a common cause of occupational exposure in the developing world. [...] We have highlighted excessive pesticide approval with poor regulatory control in Trinidad and Tobago." [pp. 84-5, 87-9]

COSTA RICA

Viales López 2014 – Majority of fatal paraquat poisonings resulting from ingestion[177]
Paraquat is a widely used herbicide and is frequently used for purposes of suicide. However it can be difficult to distinguish cases from homicide, accidental exposure or a work-related accident. The estimated minimum lethal dose for humans is 10 – 15 ml of the concentrated product and the intestinal absorption is the most important route through which have been reported most of the fatal cases. [p. 6]

Berroteran J. 2008 – Paraquat poisonings frequent with very high mortality in Matagalpa, Nicaragua[178]
Between 2005 and 2008, 388 poisonings with paraquat were recorded in Matagalpa, Nicaragua, with a very high mortality of 54 %. This is due to its high use and accessibility in this area. Among the poisoning victims, 6 % were children and adolescents under 15 years, while 66 % were 15 to 25 years old (men accounted for 72 % of these). It was estimated that 26 % of the poisonings were occupational or accidental. Based on data for 2007 recorded by the national ministry of health (MINSA), the chemical group of organophosphates accounted for most poisonings, followed by bipyridilium herbicides (paraquat and diquat) and fumigants (aluminium phosphide). Paraquat accounted for a higher proportion of self-harm cases compared to the organophosphates which were largely implicated in occupational poisonings, due to high use and working conditions. Use of paraquat for self-harm increased in the past few years and now exceeds the number of incidents with organophosphates or aluminium phosphide.

Henao S. 2006 – Plaguicidas y salud en países del Istmo Centroamericano [Pesticides and health in the Central American Isthmus]. OPS: Proyecto Plagsalud.

www.bvsde.paho.org/bvsacd/taller-toxicos/situacion.pdf

Plaguicidas responsables de la mayor morbi-mortalidad en las paises del Istmo Centroamericano [Pesticides responsible for the highest morbidity and mortality in Central America]: [...] 93. Paraquat [only prohibited in the Domenican Republic] [p. 20]

3.8 – STUDIES ON SELF HARM/SUICIDES AND PESTICIDES (paraquat not directly specified)

Bose et al 2009 – Self-harm and self-poisoning in southern India: choice of poisoning agents and prevention[179]
Surveillance over period of two years in a community of 108'000 people living in a primarily rural area of southern India.

"Poisoning and hanging are the most common modes of suicide; 110 used poisoning (43.7 %) and 107 hanged themselves (42.5), followed by 20 burning (7.9) and 14 drowning (5.6 %; Table 1, in Bose et al 2009). There was an association between mode of suicide and survival, the lethality being greater in hanging, drowning and burning, and least in self-poisoning [...]. In addition to the 46 cases of death from self-poisonings, 64 cases of non-fatal self-poisonings were recorded. [...] Pesticides were the preferred agents, 68 (61.8 %) both for suicides and attempts [...]. Of those who died after consuming poisons, 36 (78.3 %) did so after ingesting pesticides and 9 (19.5 %) after ingesting plant poisons. [...] Almost all the pesticides mentioned were class Ia, Ib or II after the WHOs classification.[1]

One of the ways that death caused by consumption of pesticides could be reduced is to limit the toxicity of the pesticides that are available for sale in the market. Such a measure seeks to reduce the lethality of the attempt, and not attempt to cause a reduction in the incidence of self-harm. The lower toxicity increase the chances of the person being found alive, and being taken for treatment, with resultant greater chances of survival. [...] The factors that we wish to highlight in this article are that, prevention at the current time can focus on restriction on the types of poisons that are available and promoting access to better health care." [pp. 762–765]

Chowdhury, Banerjee, et al 2013 – Most patients hospitalized for self harm have no psychiatric illness (India)[180]
This study examined the role of psychiatric disorders, underlying personal and social situation, and triggers of deliberate self-harm among 89 patients (23 men and 66 women) hospitalised in three primary health centers of the Sundarban Delta, India, in 2006. Most of the subjects (69.7 %) were uncertain about their "intention to die" from the self-harm act. Use of poison was by far the most frequent method in both sexes, with 100 % of females and 82.6 % of males using it, while hanging (17.4 %) was seen only among males. The majority of subjects, 63.2 % men and 66.7 % women, used commonly available agricultural pesticides.. In rural areas of India, lethal pesticides are easily available to all family members of farmers, and in many regions there is no control on sale or purchase of pesticides, nor is any safety information disseminated to farmers, while very few shops selling pesticides are licensed and pesticides are available even in grocery stores. In individuals with familial maladjustment cumulative emotional stress increases vulnerability to self-harm which highlights the need for community-based counselling and clinical attention. In many of the cases self-harm behaviour appeared to be primarily motivated by the wish to seek attention. Impulsivity may play a greater role in self-harm than was previously thought and easy access to means of self-harm has considerable impact on the decision to act (Bridge

2006). To reduce mortality and morbidity from pesticide poisonings preventive activities are needed, in particular psychosocial support at the community level, regulation of pesticide distribution, and education of farmers.

Conner KR, Phillips, et al 2005 – Restricting access to pesticides may reduce impulsive suicides (China)[181]
Women and younger individuals were more likely to carry out low-planned and intermediate-planned than high-planned acts of suicide. Greater acute stress distinguished low-planned [impulsive] from high-planned suicides. Ingestion of pesticides stored in the home was a more commonly employed method in low-planned than high-planned suicides.

Low-planned suicides are more common in women, in younger individuals, and among those who are experiencing acute stress. Prevention strategies targeted at restricting access to pesticides may preferentially lower the rate of low-planned suicides.

De Leo D. 2013 – Impulsive self harm acts using easily available lethal pestsicides increase fatality (China)[182]
"[...] we are now familiar with the fact that suicide rates are higher in rural environments; that those rates can be excepti-onally high in women, making rural China the place in the world where suicide is more frequent in females than in males; that pesticides ingestion is the most common method of suicide; that impulsivity is alarmingly common in those who exhibit suicidal behaviors; and that where pesticides are readily available (as in rural areas), non-meditated suicidal acts using high-toxicity pesticides can prove fatal if technically sophisticated resuscitation facilities are not easily accessible. [...] In this Chinese experience, the low proportion of depression and mental disorders as a whole emphasizes even more the big role of impulsivity. The agricultural context and the easy availability of lethal pesticides make the risk of fatalities particularly high."

Lee, Cha et al 2009 – Deaths from pesticide poisoning in South Korea: trends over 10 years[183]
"The number of pesticide poisoning deaths from 1996 through 2005 was 25,360 [data of Korea National Statistical Office], which accounted for 58.3 % of the total poisoning fatalities. The age-standardized mortality rates by pesticide poisoning significantly increased from 4.42 to 6.42 per 100,000 population, whereas the total death rate was decreased in the same period. Intentional self-poisoning was the majority cause of death from pesticides (84.8 % of total pesticide poisoning deaths). The majority of the pesticide poisoning deaths were men, over 50 years old, with education less than middle school, and residing in rural areas. The rate of pesticide poisoning deaths was the highest in the farming period and was significantly correlated with the rurality index of each region. [...] More intensive intervention efforts to reduce pesticide mortality should become a public health priority in South Korea."

Phillips & Gunnell 2009 – Pesticide restriction should be a key component of suicide prevention programmes[184]
"The importance of intentional ingestion of pesticides was initially recognized in Asia and the Western Pacific but it is becoming evident that it is also a significant problem in Africa and, to some extent, in Latin America. Pesticides are employed in about 300,000 suicides annually — primarily in the rural areas of low-and middle-income countries (LAMIC) — so limiting access to these lethal agents could, theoretically, substantially reduce the global burden of mortality due to suicide. [...] Given that about one third of all suicides worldwide are by pesticide ingestion, restricting access to pesticides should be a key component of the global effort to reduce suicides. Attempts to restrict access by encouraging governments of LAMIC to adopt international guidelines have had limited effect, largely because no real attempt has been made to adjust the guidelines to the resource structure and rapidly changing agricultural practices of each country or, more importantly, to understand and address the attitudes and incentives of key stakeholders in the target communities. [...] Training about safe usage by agrochemical firms often results in increased knowledge but does not necessarily result in changed behaviour (Ellis 1998; Atkins & Leisinger 2000). Moreover, this training often leads to increased market penetration of the products (the goal of the industry) and, thus, an increase in the availability of pesticides. Approaches to limiting access by improving local storage and management of pesticides – the preferred approach to restricting access of the agrochemical industry – have only recently been attempted, their long-term benefit (or harm) remain to be proven."

Vijayakumar & Satheesh-Babu 2009 – Restricting pesticide availability reduces suicide numbers in India[185]
"Four villages in the state of Andhra Pradesh in India that had stopped using chemical pesticides in favour of non-pesticide management (NPM) were visited to assess any change in suicide incidence before and after discontinuation of chemical pesticides. [...] In the pesticide-free villages there were 14 suicides before introduction of NPM and only three suicides thereafter. The percentage of suicides not reported to authorities was 47 %.

Conclusion: Restriction of pesticide availability and accessibility by NPM [non-chemical management] has the potential to reduce pesticide suicides, in addition to psychosocial and health interventions."

4

Limited worker protection in agriculture

4.1 – SYNOPSIS: ABSENCE OF EFFECTIVE PROTECTION FOR WORKERS

The *Code of Conduct*, a globally accepted standard, calls for actions to reduce the health and environmental risks of pesticides, and recommends that governments and pesticide industry should take these actions (FAO 2014).[186] Although paraquat is a particularly hazardous chemical, recommendations for worker protection published online by Syngenta, one of the main manufacturers, are unclear and appear insufficient (see: 'Five golden rules for safe use', http://paraquat.com/safety). These state: "Wear gloves, hats, masks, eye protection and waterproof aprons as prescribed" but do not specify that workers who use paraquat must wear a respirator with a particulate (dust or mist) filter.

Without respirator workers are not sufficiently protected from absorbing spray droplets through the nose or mouth during spraying. A cover over the face or mouth does not provide adequate protection from fine spray droplets, and it may become soaked. Paraquat poses a very high risk to workers who use backpack sprayers due to its very high acute toxicity and chronic health hazards. Splashes of diluted product in eyes can injure the cornea and a subsequent inflammation may impair vision. Prolonged contact with paraquat solution (e.g. due to a leaking sprayer or inadequate protection) can cause skin damage, leading to increased absorption.

Effects on the respiratory system (chronic bronchitis, shortness of breath) can occur in workers after long-term exposure to paraquat (Castro–Gutiérrez et al 1997; Dalvie et al 1999; Schenker et al 2004). Paraquat is very toxic by inhalation, and inhalation of the spray can be fatal (EC 2003; 2008).[187] Spray droplets in the air can be absorbed when a worker breathes through the mouth which is frequent during heavy labour (Frumkin 2000).[188] Large spray drops collect in the nose but can be absorbed if swallowed via the back of the nose and throat. Paraquat measured in air after spraying exceeded limits in the USA (Morshed et al 2010).[189] In at least two fatal cases of poisoning in Costa Rica spray droplets of paraquat may have been inhaled (Wesseling et al 1997).[190] It cannot be overemphasized that wearing the necessary protective equipment might beimpractical in hot climates due to heat stress, and that even very basic protection is often not available in developing countries.

To be effective it is essential that protective clothing, gloves, respirator, and safety goggles are worn correctly and are intact. If this is not the case spray solution (leaking from a defective sprayer) and droplets deposited onto clothing can penetrate the outer layer and contaminate skin. Liquid spray can collect in gloves or boots, resulting in prolonged exposure of skin to the spray solution, absorption via skin, and a high risk of poisoning. Even when workers use protective equipment as required, exposure to a pesticide during spraying cannot be eliminated. Eye injuries can occur from spills or splashes and may lead to impaired sight. Skin exposed to the diluted product or concentrate can be irritated or burnt. This may lead to increased absorption, especially if skin comes into contact with the spray solution or concentrate for a certain time. Further, no antidote against paraquat poisoning is available and chronic irreversible effects seem possible via contact to very low doses.

In 2007, the European Court of Justice annulled the registration of paraquat within the EU on the basis that "in a Guatemalan study one of the participating operators underwent exposure to paraquat equivalent to 118 % of the acceptable operator exposure level fixed for that substance, despite use under the proposed conditions. Accordingly, the Community requirements, which prohibit any exposure higher than the acceptable operator exposure level, have not been satisfied. Consequently, Directive 2003/112 fails to satisfy the requirement of protection of human health." (COJ).[191]

Additionally it must be emphasized that paraquat's very high acute toxicity, its ability to damage skin and be absorbed via skin, and absence of an antidote are particularly harzardous properties which preclude a sufficient level of protection of workers' health from being attained, even under conditions of "normal use".

4.2 – UNINTENTIONAL EXPOSURE OF HANDLERS TO PARAQUAT

Kumar, Lakshmikutty 2015 – Conditions of paraquat use in India[192]

"The study found that paraquat dichloride, a herbicide, is used for controlling weeds in at least 25 crops in India (as per infor-

mation from the study areas) whereas the Central Insecticide Board and Registration Committee (CIBRC) has approved it only for nine crops. This means that many of the uses of paraquat are in violation of the laws in India regarding pesticides. The State Agriculture Departments and/or Agriculture Universities and the various commodity boards are in violation of the law as they have recommended paraquat for crops other than those approved by the CIBRC. Similarly, Syngenta, one of the major suppliers of paraquat, has recommended the use of its product Gramoxone in 12 crops and another manufacturer Canary has recommended the use of Kataar for 11 crops, again over riding the CIBRC.

It is evident from the interviews that farmers are not fully aware of the crops on which paraquat use is approved. Though farmers are aware that paraquat and other pesticides are poison, they lacked information about its proper use. Most of the workers interviewed were also not aware of the same and lacked the required PPE, thereby, increasing the risk of exposure and poisoning. This clearly indicates the failure of the agriculture departments and other concerned government agencies in providing adequate information about the use of paraquat and the PPE.

Interestingly farmers seek and get advice not from the concerned government departments but from the retailers or the agents of companies or distributors. This has contributed to insufficient information and improper use of the herbicide. In West Bengal paraquat was being sold in plastic carry bags, further increasing the risk of spillage, exposure, and poisoning.

The study found the use of paraquat dichloride is happening in violation of the Indian Insecticides Act. In addition to the violation of the International Code of Conduct on Pesticide Management, the conditions of use of paraquat in India also violate international conventions such as the Chemicals Convention of 1990 and the Safety and Health in Agriculture Convention of 2001. The actual practices in the field indicate the absence of an effective regulatory as well as monitoring system which in turn promotes misuse and illegal practices. Paraquat is being used in unsafe and dangerous conditions at the retailer, farmer and worker level. All this is happening while numerous adverse health effects have been reported from farmers and workers due to exposure to paraquat. All these demonstrate the need to take necessary steps towards a progressive ban of paraquat in India."

Lee, Park et al 2009 – Monitoring paraquat exposure of workers in plantations in Costa Rica[193]

This study examined occupational exposure to paraquat among farm workers in Costa Rica and identified determinants of exposure. Urine samples were collected every 24 hours from 119 paraquat handlers and 54 non-handlers on banana, coffee and palm oil farms. Information was collected about the handling of product. Urinary paraquat levels were determined by enzyme-linked immunosorbent assay with limit of quantification of 2 ng/mL. Inhalable dust and airborne paraquat were simultaneously measured for a subset of participants.

"Typical work clothing consisted of long pants, long or short sleeved shirts and/or coveralls and boots. Paraquat handlers wore rubber gloves at banana and palm oil farms but not at coffee farms. [...] On the spraying day, 4 out of 53 non-handlers (7.6 %) had detectable urinary paraquat. The individual paraquat levels of the four non-handlers were 2.2, 2.9, 4.7 and 6.8 µg/24 h. [...] A total of 83.3 % (N = 45), 47.1 % (N = 56) and 63.9 % (N = 46) of the samples were below the LOQ [2 ng/mL] on before, during and after paraquat spray days, respectively [...]. Arithmetic means (± SD) and geometric means (GSD) of urinary paraquat levels on spray days were 6.3 (± 10.45) and 3.0 (3.07) µg/24 h, respectively [...] Detectable paraquat levels were significantly different by crop, with the highest proportion of exposed workers on banana farms – 75.0 % in banana, 53.9 % in coffee and 21.0 % for palm oil, ($\chi 2 = 12.5$, $p = 0.002$). [...] All workers used boots. Among handlers at coffee, banana and palm oil farms, 66.4 % wore a coverall, 38.7 % wore gloves, 38.7 % used a respirator, and 65.6 % wore an apron. Facemasks and safety glasses were rarely used. The use of PPE significantly differed by crop in this study. At banana and palm oil farms, all herbicide handlers used gloves, aprons, respirators and boots when they loaded and sprayed paraquat, and maintained equipment. At coffee farms, use of most types of PPE was low, with the exception of the use of coveralls (48.7 %), aprons (48.7 %) and boots (100 %). [...] Our data of urinary paraquat levels on before-, during- and after- spray days suggested that the majority of the absorbed paraquat is excreted within 24 h of sampling. Urinary paraquat levels on before and after spray days were significantly lower than on the spray day. [...] Since there is no conclusive data on the half-life of paraquat in humans, we applied 24-h urine sampling." [pp. 458-460]

"The arithmetic mean (±SD) and geometric mean (GSD) for airborne paraquat level measured was 6.07 (±4.77) and 4.75 (2.07) µg/m3, respectively (Table 5 in Lee, Park et al 2009). Among 25 handlers with airborne paraquat analysis, 15 (60 %) handlers had detectable urinary paraquat level. [...] Work hours for handlers were substantially shorter on the palm oil farm, where we observed lower exposures. [...] The ACGIH TLV [American Conference of Governmental Industrial Hygienists Threshold Limit Value] of paraquat level in respirable dust is 100 µg/m3." [p. 459, p. 460]

Machado-Neto et al 1998 – Potential skin exposure to paraquat from manual spraying reaches unsafe levels

Studies on the efficacy of safety measures for knapsack sprayers applying paraquat to maize were carried out. Spraying in front of the workers' body was found not to be safe. Potential skin exposure with spray was too high both when a 0.5 m long lance (shaft) a 1 m lance were used. Based on calculated margins of safety*, it was estimated that potential skin exposure needed to be reduced by 50–80 % for a 0.5 m lance, and by 37–69 % for a 1.0 m lance. Most of potential exposure arose from sprayed plants contaminating skin of legs and feet. A longer spray lance alone did not reduce potential skin exposure enough to provide safe conditions. Workers mixing/loading solutions received main exposure at the hands. Impermeable gloves should be used.

**Margin of safety:* Ratio of the highest estimated or actual level of exposure to an agent (e.g., pesticide) and the highest nontoxic dose threshold (usually the no–observed effect level or conc.) (Stephenson GR et al 2006)

Morshed, Omar et al 2010 – Estimated potential dermal and inhalation exposure above US threshold[194]

This study measured airborne paraquat and exposure of spray-operators in a test plot in Malaysia. Morshed et al (2010) found significant levels of exposure even under the relatively high safety measures in force. Airborne residues were collected from a paraquat-treated field for 12 hours at four hour sampling intervals before and after spraying, using approved sampling materials and methods. Paraquat residue was detected by HPLC with an UV detector. Pre-spray measurements did not detect paraquat. In post spray active sampling, paraquat was detected only on quartz filter samples which revealed that in the air paraquat is associated with particles rather than vapour. Paraquat air concentration was detected at higher level in first four hours. The highest paraquat air concentration measured during the 25 min spray application at operator's breathing zone was 125 µg/m3, i.e. above the threshold limit value (TLV) and the recommended exposure limit (REL) (100 µg/m3) of the American Conference of Government Industrial Hygienists and the National Institute for Occupational Safety & Health. Potential dermal and inhalation exposure doses estimated by extrapolating air residue data showed a substantially higher value than the proposed acceptable operator exposure level, 0.0005 mg/kg day.

Ochaeta Paz 2010 – Twelve most hazardous pesticides including paraquat readily available in Guatemala[195]

"The results of surveys show that the pesticides paraquat, terbufos, aluminum phosphide, ethoprophos, methyl parathion, endosulfan, carbofuran, monocrotophos, methomyl, chlorpyrifos and aldicarb – RESSCAD restricted by the 2000 Agreement – are being marketed by pesticide dealers in Guatemala city. Vendors to not check whether purchasers have documentation which entitles them to purchase pesticides, and they do not provide information necessary for the use and handling of pesticides. In addition there is no awareness about their toxicity [...]."–

Wongwichit 2010 – Can improved risk communication affect paraquat poisoning symptoms significantly?[196]

Maize farmers in Thailand were questioned about their knowledge, attitudes and practices of pesticide use. In a later phase this study assessed if an improved communication of the risks resulted in lower exposure levels: "The majority of maize farmers have high knowledge, positive attitude, good practices, but maize farmers still have poisoning toxic symptoms due to pesticide exposure because some farmers did not use PPE [personal protective equipment] and some farmers used improperly PPE. [...] After intervention, paraquat residues more than 0.2 1 mgl/l were detected in 4 cases (7.8 %) of experimental group and 11 cases (19.0 %) of control group. [...] the proportion of paraquat poisoning toxic symptoms between group after intervention were significantly difference in burn nose, eye irritation, tear drop, and mucus symptoms [...] Risk communication model may not affected to significantly decrease paraquat residue and paraquat poisoning toxic symptoms after intervention in the experimental group when compared with the control group." [p. v]

A farmer with a hand operated sprayer (West Bengal). Often paraquat and other pesticides are applied with this kind of sprayer. | © Dileep Kumar A. D.

4.3 – PRACTICAL LIMITATIONS OF PERSONAL PROTECTIVE EQUIPMENT

Baharuddin et al 2011 – Paraquat exposure among Malaysian farmers via inhalation and skin exposure[197]

"...windspeed had the strongest impact on pesticide exposure via inhalation. However, the degree of exposure to both herbicides via inhalation was below the permissible exposure limits set by United States National Institute of Occupational Safety and Health (NIOSH) [0.1 pp. for paraquat]. Dermal Exposure Assessment Method (DREAM) readings showed that dermal exposure with manual spraying ranged from moderate to high. With motorized sprayers, however, the level of dermal exposure ranged from low to moderate. Dermal exposure was significantly negatively correlated with the usage of protective clothing [PPE]. Various types of deleterious health effects were detected among users of manual knapsack sprayers. [...] Respondents using motorized sprayers showed higher mean concentration of [inhalation] exposure to both herbicides than those using manual sprayers. Those respondents, using either motorized or manual sprayer, who showed high mean inhalation exposure improperly used PPE [personal protective equipment]. [...]

The dermal exposure of respondents that used manually operated spraying equipment was found to be moderate (30.99–99.99 Dermal Unit [DU]) to high (100.00–299.99 DU) while respondents using motorized sprayers came under the very low (10.99–29.99 DU) to moderate exposure (30.99–99.99 DU) category. [...] the mean dermal exposure to both pesticides using both types of spraying equipment was much higher for respondents adopting improper use of PPE. [...] The exposed group showed a higher mean level of both liver enzymes [ALT and GGT] compared to that of the non-exposed group. [...] The results for deleterious health effect variables [nausea, excessive sweating, imprecise movement, numbness, reddish face, and skin itchiness] showed a higher percentage of occurrences for the exposed group than for the non-exposed group. However, no significant difference ($P > 0.05$) was found with regards to health symptoms related to neuro-behavioural disorders, that is, (i) difficulty in concentrating, (ii) sleep disturbance, (iii) stress, (iv) vomiting, (v) loss of grip strength, (vi) finger tingling and (vii) eye itchiness. [...] The most significant health effects reported among the pesticide handlers were difficulty in concentrating, numbness, excessive sweating, skin itchiness and slower body movements. The high and abnormal levels of the liver enzymes ALT and GGT were observed, probably due to long-term exposure to pesticides." [p. 600, pp. 605-6]

Murphy 2001 – Inadequate understanding of paraquat's risks among users following training by industry[198]

"A self-survey among paraquat users in Sumatra regarding how they handle it and its health effects was conducted in 3 field meetings among 90 corn producers. The results were tallied on the spot, question by question, explaining the rationale of each. Although many of them claimed they had had industry paraquat handling training in the past, they had never understood its specific risks and hazards (pulmonary fibrosis, dermatitis)."

Yang, Wang et al 2014 – Farmers use inadequate protective measures farmers in two rural areas of China[199]

Farmers in two rural areas of China were questionned about their awareness of risk mitigation measures for using pesticides. Protective measures were inadequate: 65 % (in Qianyang County) and 55 % (Chencang County) of farmers never used any protective measures during pesticide spraying. Washing the hands was the most common mode of personal hygiene (over 70 %); only 26 % and 30 %, respectively, of farmers used waterproof clothes, and few farmers used masks and gloves. About 20 % farmers responded that they took no precautions after applying pesticides. A large proportion, 84.7 % and 79 %, respectively, discarded empty containers near fields, and containers were also burnt or buried. Although some protective measures are taken, farmers seem unaware of the true risks of using pesticides. Retailers were well-informed and had a better understanding of pesticide application. Strict procedures for pesticide registration should be considered, details on pesticide toxicity for humans included on labels, supervision and environmental monitoring should be strengthenend, and safety practices during pesticide use surveyed at the national scale and the risk evaluated. Paraquat was among the pesticides used in the two areas at the time when the study ways conducted.

EXPOSURE TO MULTIPLE PESTICIDES (paraquat not directly specified)

Baldi et al 2006 – Personal protective equipment reduces pesticide exposure to a limited extent[200]

"The contamination increased with the number of spraying phases and when equipment cleaning was performed. Types of equipment influenced significantly the daily contamination, whereas personal protective equipment only resulted in a limited decrease of contamination. [...] Spraying resulted in the highest contamination, but not proportionally to its duration: indeed, spraying corresponded to 54 % of the contamination but to 80 % of the treatment duration. Equipment cleaning, which corresponded to the shorter operation (7 % of the duration), resulted in a median concentration intermediate between spraying and mixing operations. The part of the contamination during equipment cleaning was even responsible for the majority of exposure in some subjects [...] The contamination of the hands was the highest in all tasks performed, as expected from other studies. Even for subjects with gloves the contamination was quite high. This result is certainly explained by the fact that subjects were left free either to use or not to use gloves and to choose their own gloves, possibly old ones." [pp. 116, 123]

Feola et al 2012 – Educating workers about protective measures may result in limited adoption in practice[201]

"...education is often proposed to promote safer practices. However, evidence point to limited effects of education. [...] the results suggest that, under these conditions, no policy is able to trigger a self sustaining behavioural change."

Evans et al 2001 – Personal protective equipment and dermal exposure[202]

"Studies of workplace protection suggest that the spread of contaminants inside protective clothing, including gloves, is commonplace and significant. Insufficient attention may have been paid to the effect of factors such as temperature differentials on the permeation of chemical agents through protective materials."

Garrod et al 2003 – Skin exposure is very common and uptake via skin important also with PPE[203]

"The pathways for dermal exposure may be summarized as one or more of:

- Primary exposure (direct contact); this includes hand immersion.
- Primary exposure (deposition); contaminants impact or settle on the skin by splash, aerosol deposition or by penetrating clothing.
- Secondary exposure (indirect contact); skin contact with contaminated objects or surfaces. [...] post-use, when secondary skin exposure (e.g. contact with contaminated PPE) is likely to occur.

Even transient dermal exposure can lead to prolonged uptake [...] Any penetration of coveralls or protective gloves leads to prolonged exposure. [...] chemical agent (pesticide) penetration inside protective gloves was common, if not inevitable, for dusts, water-based and solvent-based products alike (Garrod et al. 2001). More recent research has shown that much of this penetration occurs the second time that a pair of chemical protective gloves is put on. The hands become exposed through handling contaminated gloves. The resultant hand exposure inside gloves is prolonged and occluded (Rawson et al. 2002). It is clear that dermal exposure is practically inevitable when using chemicals outside containment, even using PPE (HSE 1999; HSE 2002). As proposed above, it is not practicable to differentiate duration, as prolonged uptake can follow transient exposure. [...] a significant proportion of the total skin exposure to chemical agents is likely to occur inside protective gloves. The estimated actual total dermal exposures are ~500 mg/h for dipping and for spraying. This is of concern for both solids and liquids in all dermal hazard bands." [p. 582]

HSE 2013 – Limited effectiveness and reliability of personal protective equipment (PPE)[204]

"Some control options are inherently more reliable and effective than others. For example, the protection afforded by PPE is highly dependent on good fit and attention to detail. [...] There is a broad hierarchy of control options available, based on inherent reliability and likely effectiveness. [...] They include:

- elimination of the hazardous substance;
- modification of the substance, process and/or workplace;
- applying controls to the process, such as enclosures, splashguards and LEV [local exhaust ventilation];
- working in ways that minimise exposure, such as using a safe working distance to avoid skin exposure;
- equipment or devices worn by exposed individuals. [...]

PPE tends to be less effective and reliable than other control options because it:

- has to be selected for the individual;
- has to fit the individual and not interfere with their work or other PPE worn at the same time;
- has to be put on correctly every time it is worn;
- has to remain properly fitted all the time the individual is exposed;
- has to be properly stored, checked and maintained;
- tends to be delicate and relatively easily damaged;
- can fail without warning;
- may provide no protection when it fails." [pp. 31-2]

Macfarlane 2013 – Poor compliance with requirements for PPE among occupational user of pesticides[205]

"Evidence for the effectiveness of safety training in the promotion of personal protection is contradictory (Reynolds et al 2007), and it is likely that local factors including the quality and content of safety training and the receptivity of the audience may vary in different local contexts. [...] exposure presents a significant health risk to workers involved in the end use of pesticides. The majority of pesticide absorbed into the body comes from dermal exposure, and PPE in the form of appropriate gloves and clothes has been shown to reduce absorption. However, compliance among the majority of occupationally exposed pesticide end users appears to be poor. The reasons for poor compliance are not clear and, although training appears promising, there is poor understanding of the delivery modes, content, and teaching methods that are most effective." [p. 140]

Sarr & Thiam 2011 – Community-based monitoring of health impacts in Senegal[206]

"The pesticides users are often illiterate and don't wear adequate protective personal equipment (PPE) when spraying pesticides. The cotton farmers are often untrained and unaware of health and environmental impacts of pesticides. They often store pesticides within their homes and re-use the empty pesticide containers as water vessels. 95 % of those interviewed did not use PPE, while more producers spray against the wind (74 %) than with the wind. The farmers report a number of health symptoms after spraying pesticides, most commonly headaches (61 %), blurred vision (59 %), excessive sweating (57 %) and nausea and vomiting (23 %)."

5

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FURTHER STUDIES FROM BEFORE 2010 ARE DISCUSSED IN THE FOLLOWING PUBLICATIONS:

Marrs & Adjei 2003 (see section 7.1)
Neumeister & Isenring (2011); Watts (2011) (see section 7.2)
Wesseling et al 2001 (see section 7.4)

Endnotes

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