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Paraquat poisoning following the introduction of the European Union ban

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Abstract

Aim

The aim of this study was to examine and characterise all paraquat poisoning cases reported to the National Poisons Information Centre of Ireland (NPIC) over a 23-year period (1999-2022), and to compare data from the periods before and after the implementation of the ban, to determine its impact.

Methods

This is a prospective observational national population study on consecutive human cases reported to the NPIC following the introduction of the EU paraquat ban. Since 01/01/1999, the NPIC prospectively collected data from all cases of paraquat poisoning for the purposes of a longitudinal epidemiological study of paraquat poisoning in Ireland. Thus, data that had already been collected prospectively in the pre-ban period (1999-2008) served as baseline comparative data for this observational study. Inclusion criteria consisted of all cases of ingestion of paraquat-containing products. Exclusion criteria consisted of cases of dermal, ocular and inhalational exposures only.

Data collected included: patient demographics, exposure circumstances (classified as intentional/deliberate or unintentional based on the history provided at the time of the enquiry to the NPIC), product formulation, clinical features, detection of paraquat in biological fluids, and patient outcome (determined from follow-up telephone enquiries to the treating hospital). Our primary outcome measure was the observed effect of the EU paraquat ban on the incidence of paraquat poisoning cases in Ireland pre-ban and post-ban. Secondary measures included the circumstances (intentional versus unintentional, the type of product used pre and post ban), and the toxicity, morbidity and mortality of paraquat poisoning in Ireland.

Results

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Prior to the introduction of the European ban (1999-2007), there were 95 cases of paraquat poisoning (70 intentional, 25 unintentional) with 33 fatalities. Following the ban (2008-2022), there were 11 cases of intentional poisoning with 4 fatalities, and no cases of unintentional poisoning. Since 2014, there have been no further poisoning cases reported in Ireland. A small reduction in the hospital mortality rate for intentional overdoses pre/post-ban was observed; 47.14% (33/70) for 9-years before the ban compared to 36.36% (4/11) following the paraquat ban. Whilst this small reduction in fatality rate was not clinically significant, the real-term fatality numbers were, with an observed reduction in fatalities from 33 in the nine years prior to the ban, to 4 in the fourteen years since the introduction of the EU ban. A **c**omparison of the 3-year moving average number of paraquat poisoning cases indicated the EU paraquat ban significantly reduced the number of poisoning cases.

Discussion

Globally, public health measures that were introduced by manufacturers, policy makers and governments to ensure occupational safety, failed to prevent paraquat poisoning.

In our study, paraquat poisoning resulted in significant morbidity and mortality especially with professional formulations, reflecting other epidemiological research findings. The majority of patients with a fatal outcome (24, 64.87%) died within 24-hours.

Importantly, there were no further cases of unintentional paraquat ingestion following the European ban and the incidence of intentional poisonings was notably reduced. The evidence from this observational study demonstrates that the paraquat ban has been a successful public health measure in Ireland.

The European Union legislation revoking paraquat's licence was a successful public health intervention that eliminated unintentional paraquat exposures and effectively reduced the incidence of deliberate poisonings and fatalities in Ireland.

Introduction

Paraquat (1,1'-dimethyl-4,4'-bipyridinium) is a non-specific contact herbicide, available commercially since 1961.[1,2] Paraquat is commonly used in deliberate self-harm and suicide attempts and is associated with high morbidity and mortality due to its inherent toxicity and lack of effective treatments.[3,4] Multi-organ failure, cardiogenic shock and death can occur following ingestion of concentrated paraquat, while pulmonary fibrosis and respiratory failure can develop with lesser amounts.

Global safety concerns prompted legislative, manufacturing and educational initiatives to control paraquat's availability and prevent poisoning, with limited impact. During the 1980-1990s, several European countries introduced legislation banning paraquat including Sweden (1983), Finland (1986), Hungary (1991), Austria (1993), Denmark (1995), and Slovenia (1997)[1]. In 2005, non-professional paraquat-containing products (with lower paraquat concentrations) were withdrawn from sale in the European Union (EU). In 2007, following a judgment of the European Court of First Instance, authorisation for the sale and/or supply of professional paraquat products, containing higher concentrations, was revoked throughout the EU.[5] Given the previous ban on non-professional products, this effectively resulted in an EU-wide ban on all paraquat-containing products. A phase-out period permitted the sale of existing supplies until 2008.

Despite the ban applying throughout the EU since 2007, data on its impact remains limited. The study aimed to evaluate all cases of paraquat ingestion reported to the National Poisons Information Centre of Ireland (NPIC) from 1999-2022, and to compare data before and after the implementation of the ban, to determine its impact.

Methods

This was a prospective observational national population study on consecutive human cases reported to the NPIC following the implementation of the EU paraquat ban. The study was registered with the Office of Clinical Audit (CA2022/124), and as a service evaluation, ethics committee approval for publication was waived.

Since 01/01/1999, the NPIC prospectively collected data from all cases of paraquat ingestion for a longitudinal epidemiological study of paraquat poisoning in Ireland. Thus, data that had already been collected prospectively in the pre-ban period (1999-2008) served as baseline comparative data for this observational study. Inclusion criteria were all cases of ingestion of paraquat-containing products. Exclusion criteria included cases of dermal, ocular and inhalational exposures only.

Data collected included: patient demographics, exposure circumstances (intentional or unintentional), product formulation, clinical features, paraquat analyses in biological fluids, and patient outcome (determined from follow-up telephone enquiries to the hospital). All patients were followed up whilst they remained in hospital. Outcome categories were recovery, sequelae or fatality. Our primary outcome measure was the observed effect of the EU paraquat ban on the incidence of paraquat poisoning cases in Ireland pre-ban and post-ban. Secondary measures included the circumstances (intentional versus unintentional, type of product), and the morbidity and mortality of paraquat poisoning.

Professional products available in Ireland during the study period were Gramoxone® (200g/l), Gramazine® (100g/l), Gramanol® (110g/l), Total® (200g/l), and Terraklene® (100g/l). Non-professional products were Weedol® (sachet 2.5g/l) and Pathclear® (granules 2.5%w/w).

Results

The NPIC was consulted on 106 patients who ingested paraquat during the 23-year study period [Figure 1]. Patient demographics are presented in Table 1. Intentional self-poisoning predominated with 81 cases (76.41%). Professional products (Gramoxone®, Gramazine®, Total®) were implicated in 37 (45.68%) intentional poisonings, non-professional products (Weedol®, Pathclear®) in 22 cases (27.17%), whilst the product name was not specified/unknown in 22 cases (27.17%).

The majority of patients were symptomatic [Table 1]. The predominant features were vomiting, dysaesthesia, and pharyngitis [Table 2]. 98 cases (92.45%) were successfully followed up to determine clinical outcomes. There were 37 in-hospital fatalities. 2 patients developed sequelae; one suffered oral burns and hypoxia; one developed pulmonary fibrosis and required palliative care. 59 patients recovered following acute poisoning. The outcomes were unknown for 8 patients (3 cases were not followed-up, 2 patients left hospital against medical advice; 2 patients were untraceable, and 1 patient was referred to a hospital emergency department but the NPIC was not contacted subsequently). The long-term outcomes for 2 patients who developed sequelae were not determined. Confirmatory laboratory analyses were performed in 49/81 patients following intentional ingestion (60.49%). Of these 33/49 (67.35%) had a positive urine-dithionite test and 28/49 (57.14%) had serum paraquat concentrations quantified [Table 3].

There were 25 cases of unintentional paraquat ingestion including 14 paediatric cases (<14 years). Professional products were ingested in 14/25 cases (56%), non-professional products in 8 cases (32%) and the product name was unknown in 3 cases. 12 (48%) unintentional ingestions were symptomatic. Paraquat analyses were performed for 14 cases (56%); positive results were reported in urine (n=2) and serum (n=1) [Table 3].

Overall, the in-hospital fatality rate was 34.91% (n=37). 34 fatalities occurred following deliberate ingestions, 3 patients died following unintentional exposure. Professional paraquat products were implicated in at least 70.27% of fatalities (n=26). The formulation was unknown for 11 cases. 64.9% of fatal cases died within 24-hours of ingestion [Table 4].

Before the introduction of the European ban (1999-2007), there were 95 cases of paraquat poisoning (70 intentional, 25 unintentional) with 33 fatalities. Following the ban (2008-2022), there were 11 cases of intentional poisoning with 4 fatalities, and no unintentional

poisonings. Since 2014, there have been no further poisoning cases reported in Ireland. A small reduction in the hospital mortality rate for intentional overdoses pre/post-ban was observed; 47.14% (n=33/70) for 9-years pre-ban compared to 36.36% (n=4/11) post-ban. Whilst this reduction in fatality rate was not significant, the real-term fatality numbers were, with an observed reduction in fatalities from 33 in the nine years pre- ban, to 4 in the fourteen years since the EU ban. A comparison of the 3-year moving average number of cases of paraquat poisoning pre- and post paraquat ban showed a statistically significant difference (U = 91.0, p = <0.001), indicating that the EU ban on paraquat significantly reduced the number of poisoning cases [Figure 2].

Discussion

Paraquat poisoning caused significant morbidity and mortality in Ireland for over 50-years and 325 paraquat-related fatalities have been recorded by the NPIC since 1967.[6] This was despite legislative and regulatory changes to control its use and availability. In 1968, legislation stipulated that paraquat could only be sold by authorised persons (namely 'pharmaceutical chemists' and 'persons licensed to sell other poisons'), and agricultural users required a license for professional products.[7] Furthermore, packaging and labelling requirements stipulated that the container displayed the word 'poison' and warnings that the contents 'should not be taken,' 'should be kept out of the reach of children, and not repacked from the original container'.[7] In 1970, despite the Irish government calling for the introduction of a paraquat ban, legislation never progressed.[8] In 1971, paraquat manufacturers printed warnings in the national press, restricted the number of distributors, and wrote to 260,000 famers to reinforce the labelling advice.[9] Despite these measures, 44 paraquat fatalities (including 7 unintentional ingestions) occurred from 1969-1973.[10] Decades later, paraquat fatalities continued, accounting for 21.2% (n=32) of fatalities reported to the NPIC from 2000-2012.[11]

Globally, public health measures introduced by manufacturers, policy makers and governments to ensure occupational safety, failed to prevent paraquat poisoning.[12] Research demonstrated that simply increasing awareness of paraquat's toxicity among agricultural workers is unlikely to contribute meaningfully to a reduction in paraquat suicides.[13] Measures aimed at reducing the poisoning incidence included product re-formulations with the addition of emetics, stenching agents, purgatives and chemogenic agents, with limited impact.[1,10,14,15] For example, Gramoxone INTEON® incorporates an alginate, emetic and purgative which slows absorption and allows more time for emesis. With poisoning, this product significantly reduced mortality and increased three-month survival compared with standard paraquat formulations.[16] However, paraquat-related fatalities have continued.[14,17]

Several authors have advocated strict regulation of paraquat's accessibility to prevent impulsive suicides. In one Korean study, 38.4% (n=96) of patients who attempted suicide with paraquat intentionally selected it, whereas the majority (61.6%) were influenced by its availability.[18] The authors concluded that decreasing accessibility would help suicide prevention. Another approach advocating the use of dilute paraquat solutions was discounted in a study by Nagami et al.[19] In 1986, Japan suspended sales of professional products and replaced them with products containing 5% paraquat and 7% diquat. Reduced sales caused a decrease in paraquat poisoning cases but not fatalities.[19] In Malaysia, a paraquat ban was introduced in 2002, but reversed four years later following industry pressure. When the ban was reversed, paraquat poisonings reported to the PIC doubled, and in 2008 there were seven times the number of poisoning cases compared to the period of the ban, demonstrating that availability and accessibility influenced self-poisoning.[20] Tan et al. described the epidemiology of paraquat poisonings in Malaysia from January 2008 to October 2011, following the reversal of the paraquat ban. Intentional ingestion predominated (69.6%) and the authors stated that the lifting of the paraquat sales ban facilitated suicides. 26.6% of cases were unintentional paraquat poisonings resulting in 5 fatalities. Unintentional poisonings may have been prevented if the paraquat ban had been upheld.[21]

In our study, paraquat poisoning caused substantial morbidity and mortality, reflecting other studies[3,14]. Most patients with a fatal outcome (n=24, 64.87%) died within 24-hours. This corresponds with ingestion of professional products and verified by toxicological analyses in 15 cases. Importantly, there were no cases of unintentional paraquat ingestion following the EU ban and the incidence of intentional poisonings was notably reduced, demonstrating that the paraquat ban has been a successful national public health measure.

Data on the impact of the EU paraquat ban are limited. The United Kingdom's toxicovigilance pesticide study showed a reduction in paraquat exposures comparing 2006-2007 with 2012-2013.[22] The decrease may be related to the impact of the ban, but this theory was not developed. Kervégant et al. retrospectively analysed enquiries to the Marseille PIC over 9-years including four and a half years pre- and post-ban.[23] The authors acknowledged that it was difficult to draw firm conclusions as the data were not representative of the national epidemiologic pattern for France. The Marseille PIC has a catchment population of 9 million including the south-east of France and Overseas-French-Territories (OFT). There was a reduction in unintentional paraquat poisonings but no change in the number of intentional suicides, most of which occurred in OFT. The authors proposed that the OFT agricultural community knew the dangers of paraquat and purposefully chose it for deliberate self-harm. Product availability was an important factor as people in OFT could obtain paraquat from neighbouring countries where it was not banned. The results of their study contrasts with our national experience. Before the ban (1999-2007), NPIC was consulted on 70 cases of intentional poisoning and 25 cases of unintentional poisoning. Following the European ban, there were 11 cases of intentional poisoning (presumably with existing paraquat stocks), no

further cases of unintentional poisoning. No paraquat poisonings have been reported to the NPIC since 2014, 7 years after introducing the ban.

The reliance on paraquat in non-EU agricultural countries, particularly in Asia, is likely to continue, and introducing a ban would be challenging. However, South Korea banned paraquat production and sales 2011 and 2012 respectively. Ko et al. evaluated the effect of the paraquat ban on the epidemiology and mortality and of herbicide-related poisoning (for paraquat, glyphosate and glufosinate). For paraquat poisoning cases, the mortality rate decreased (74.9% pre-ban versus 67.3% post-ban). Furthermore the paraquat ban was associated with a reduced mortality rate of herbicide poisoning.[24]

In Sri Lanka, the restriction of access to high toxicity pesticides including paraquat was associated with a reduction in pesticide suicide mortality and suicide mortality.[25] This data highlights the impact of paraquat prohibition as a suicide prevention strategy.
Given the serious consequences of paraquat poisoning, effective safety strategies and collaborative prevention efforts are needed to protect public health. Our surveillance data demonstrate that a paraquat ban is an effective method to eliminate unintentional poisoning and reduce intentional self-poisonings and fatalities.

There are some minor limitations of this research. The NPIC relies on voluntary reporting of poisoning cases however, we are confident that we would have been consulted about most paraquat poisonings given its toxicity. Paraquat analyses were not routinely available limiting accessibility to confirmatory results. A small number of patients were lost to follow-up and long-term follow-up of survivors was not conducted to determine sequelae. Analysis of national suicide data were not included.

Despite the limitations, this data shows that the EU legislation revoking paraquat's licence was a successful public health intervention that eliminated unintentional paraquat poisoning and reduced the incidence of intentional poisonings and fatalities in Ireland.

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Figure 1: Annual enquiries for paraquat poisoning and fatalities from 1999-2022.

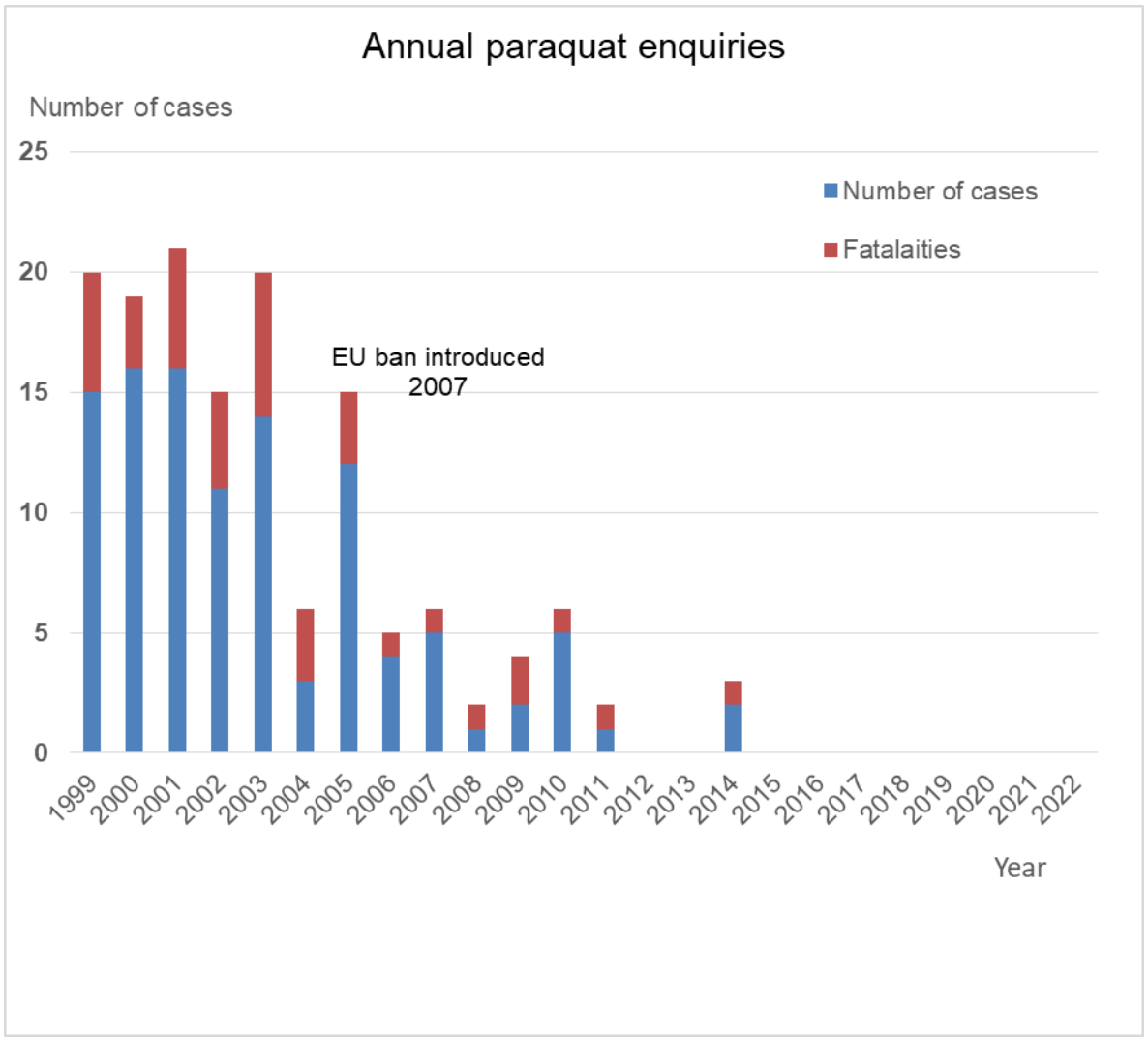

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Table 1: Patient demographics.

	Unintentional ingestion	**Intentional ingestion**
Number of patients (n=106)	25	81
Male Female Unknown	15 8 2	61 20
Adults >14 years (n)	14 (56%)	81 (100%)
Children <14 years (n)	11 (44%)	0
Mean age (years)	16.8 years *3.5 years for those aged <14 years	48.5 years
Age range (years)	1-65	14-77
Symptomatic cases (n, %)	12 (48%)	69 (85.19%)
Asymptomatic cases (n, %)	12 (48%)	10 (12.34%)
Clinical effects unknown (n, %)	1 (4%)	2 (2.47%)

Table 2: Predominant clinical features.

Symptoms	Unintentional ingestion n	Intentional ingestion n	Total n
Vomiting	2	32	34
Dysaesthesia	3	22	25
Pharyngitis	1	12	13
Respiratory effects	1	11	12
Buccal burns	4	6	10
Renal impairment	1	7	8

Table 3: Paraquat analyses.

Result	Unintentional ingestion (n=25)	Intentional ingestion (n=81)
Urine positive	2 (8%)	33 (40.74%)
Urine negative	12 (48%)	9 (11.11%)
Not available (urinalysis)	11 (44%)	39 (48.15%)
Serum positive	1 (4%)	28 (34.57%)
Serum negative	4 (16%)	4 (4.94%)
Not available (serum analysis)	20 (80%)	49 (60.49%)

Table 4: Time to death for fatal cases

Time post ingestion	Unintentional ingestion (n)	Intentional ingestion (n)	Total % (n=37)
1-4 hrs	0	15	40.54%
4-12 hrs	0	7	18.92%
12-24 hrs	0	2	5.41%
>24 hrs	3	5	21.62%
Unknown time	0	5	13.51%
Total	**3**	**34**	**100**

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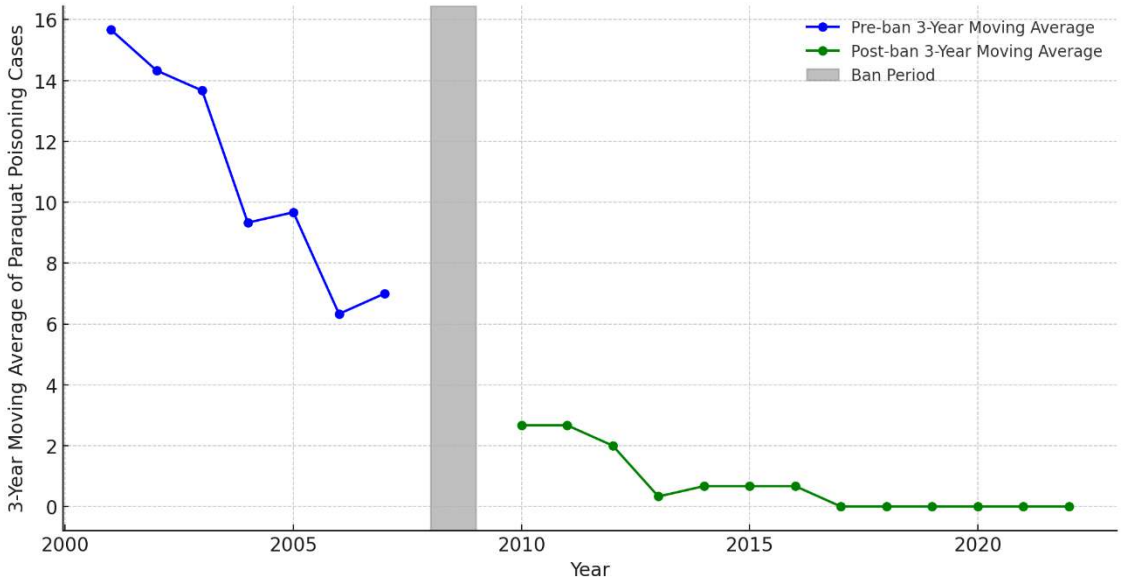

Figure 2: Comparison of 3-year moving average number of cases of paraquat poisoning reported to the National Poisons Information Centre before and after the paraquat ban. The blue line represents the pre-ban period (2001-2007), and the green line represents the post-ban period (2010-2022). The grey shaded region indicates the period when the ban was introduced. The difference in moving averages between the pre-ban and post-ban periods was assessed using the Mann-Whitney U test. The results showed a statistically significant difference (U = 91.0, p = <0.001), indicating that the EU ban on paraquat significantly reduced the number of poisoning cases. All statistical analyses were performed using Python (version 3.8.16).

Declarations of Conflicts of Interest:
None declared.

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