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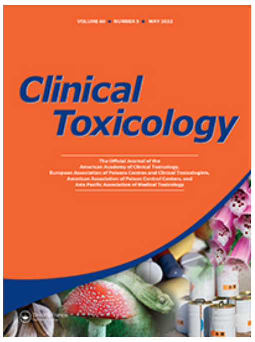

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Pesticide use, agricultural outputs, and pesticide poisoning deaths in Japan

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ABSTRACT

Objective: Although pesticide poisonings occur worldwide, most high-income countries have not been severely affected. Japan is a key exception, with pesticide suicides becoming a major public health concern in the 1980s. We here report the epidemiology of lethal pesticide poisoning in Japan in relation to its pesticide regulation and agricultural output.

Methods: We obtained data on pesticide registration and sales from the Japan Plant Protection Association's annual Pesticide Handbook, National Food and Agricultural Materials Inspection Center, and Food and Agriculture Organization of the United Nations. Data on deaths due to pesticide poisoning and population were obtained from Vital Statistics of Japan. We reviewed the registration status and hazard classification of pesticides in Japan and analysed the relationships between the use/sales, pesticides fatalities, and agricultural output.

Results: Five hundred and twenty-nine pesticide active ingredients are currently registered in Japan, including four WHO hazard class IB organophosphorus and carbamate insecticides. Paraquat was registered in 1962 as a liquid SL20 formulation. In 1986, restrictions were imposed on its sale/use and a 4.3% paraquat ion/4.1% diquat ion combination product registered by ICI. There were 221 pesticide poisoning fatalities in 2019, down from 2648 in 1986, a 92% reduction over 33 years. Self-poisoning was responsible for most pesticide deaths in both 1985 (2013/2476, 81.3%) and 2019 (146/221, 66.1%). Pesticide poisoning made up 8.6% of all suicides in 1985, down to 0.7% in 2019. Unintentional pesticide poisoning deaths also all fell by 83.8%, from 463 to 75. These reductions were associated with reduced sales of both OP/carbamate insecticides and paraquat/diquat but no apparent change in agricultural output across a broad range of crops.

Conclusions: Reduced use of highly hazardous pesticides and lowered concentration formulations in Japan were associated with major decreases in all deaths from pesticide poisoning and the proportion of all suicides due to pesticide ingestion.

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Paraquat; diquat; organophosphorus; fatality; Japan

Introduction

Pesticide self-poisoning is a major global public health problem that kills at least 110–168,000 people each year, the majority in Asia [1–3]. Most deaths have occurred in rural parts of low- and middle-income countries (LMIC) after the introduction of acutely toxic highly hazardous pesticides into agricultural practice in communities unable to safely store or use these toxic compounds [4,5]. However, several high-income countries such as Japan [6,7], Taiwan [8,9], and South Korea [10,11] have also had substantial problems with pesticide suicides.

In the 1960s, multiple organophosphorus (OP) insecticides were registered in Japan (Box 1) and OP insecticide poisoning became a grave issue for rural medicine [7,12–15]. Subsequently, the very high case fatality from self-poisoning with liquid paraquat SL 20% formulations, as well as the rapidly increasing number of deaths in the early 1980s (Figure 1, [16]), were recognised as posing particularly serious public health problems [16–20]. In the 1980s, further social issues were recognised as paraquat deaths began to occur not only from self-harm but from homicide, unintentional poisoning (especially in children) and occupational exposure [21,22]. In 1986, sales of paraquat SL20 products were suspended and replaced with a low concentration paraquat and diquat liquid combination product (Preeglox L; paraquat 4.3% paraquat ion/4.1% diquat ion combination).

The effect of trends in pesticide use and pesticide regulations on both agricultural yields and pesticide suicide numbers in Japan has not been reported. We therefore searched government data to assess associations between pesticides used in agriculture and pesticide deaths. As most pesticide deaths resulted from poisoning with OP or carbamate insecticides and the bipyridyl herbicides paraquat and diquat, this paper focuses on these two classes of pesticides.

Methods

Data on pesticides registered in Japan in 2020 were obtained from the Japan Plant Protection Association's annual

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Box 1. Pesticide registration processes in Japan.
The Agricultural Chemicals Control Law of Japan [31] was promulgated in 1948. Manufacturers apply to register their products through the Ministry of Agriculture, Forestry and Fisheries (MoAFF). MoAFF's Pesticide Subcommittee of the Agricultural Materials Committee reviews the application form and, if no problems are identified, the pesticide is registered in Japan. These procedures are repeated three-yearly to renew the registration.
When MoAFF recognizes that a pesticide is associated with a serious problem, it suggests to the company that it suspends its manufacture and registration. Manufacturers then do not typically submit the next three-yearly application to MoAFF, although exceptions sometimes occur. For example, suspension of paraquat SL20 products was suggested in 1986 but registration of these products has continued, although sales have markedly decreased.

Pesticide Handbook [23]. Identification of pesticides with lapsed registration was obtained from the Food and Agricultural Materials Inspection Center website [24]. Pesticides were catalogued as registered, lapsed, or never registered in Japan and by the WHO's classification of pesticides by hazard [25].

Data on the use of organophosphorus (OP) and carbamate insecticides, herbicides and fungicides, and all pesticides from 2000 were downloaded from the pesticide use database of the Food and Agriculture Organization of the United Nations (FAO) (http://www.fao.org/faostat/en/#data/RP). Sales statistics for paraquat and diquat from 1965 were available in the annual Japan Plant Protection Association's Pesticide Handbook [23]; however, similar data for OP and carbamate insecticides were not available due to the very large number of products used in Japan and the absence of electronic data. National annual output data for rice paddy, vegetables and orchard fruit crops from 1995 to 2016 were downloaded from the FAO website (http://www.fao.org/faostat/en/#data/QC).

The number of deaths due to OP and carbamate insecticides (International Classification of Diseases version 9 [ICD-9] code 989.3; ICD-10 code T60.0), herbicides or fungicides (ICD-9 not classified; ICD-10 code T60.3), all pesticide (ICD-9 codes 989.2, 989.3, 989.4; ICD-10 code T60), and pesticide suicides (ICD-10 code X68) were obtained from the Vital Statistics of Japan [26]. The cause of death is reported by clinicians to municipalities; the Ministry of Health, Labor and Welfare collects and classifies these data according to the ICD code, reporting the results in this report. The sub-classification of pesticide deaths by the pesticide class responsible was determined by the ICD version being used, with no sub-classification before ICD-9's introduction in 1979 and only OP/carbamate insecticides recognised as a sub-class up to ICD-10's introduction in 1995. No more refined classification of causes of pesticide poisoning by agent is available from official records.

Data for Japan's population and unemployment rate were obtained from online sources. We calculated annual mortality rates per 1,000,000 population.

We used Prais-Winsten regression models, adjusting for year and unemployment rate, to estimate the associations of pesticide sale or use with mortality rate, accounting for first-order autocorrelation in time-series data [27]. Analyses were conducted using Stata 15.0 (StataCorp, College Station, TX).

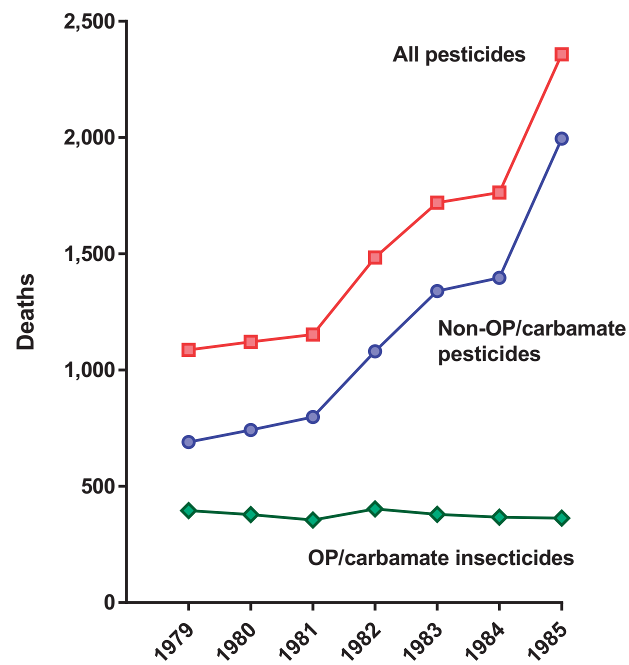

Figure 1. The increasing problem of paraquat poisoning deaths in Japan during the early 1980s. Adapted from Naito and Yamashita [16].

Results

Registration of pesticides

Five hundred and twenty-nine pesticide active ingredients are currently registered in Japan, of which 180 are insecticides, 144 herbicides, 138 fungicides, 35 growth regulators, and 4 rodenticides [23].

Of the WHO hazard classes Ia and Ib [25], only three class Ib OP insecticides, and one class Ib carbamate insecticide, are now registered (Table 1). The registration of 12 WHO Hazard Class Ia/Ib OP or carbamate insecticides has lapsed. In WHO Hazard Class II category, 13 OP and eight carbamate insecticides are registered in Japan [23], with two OP insecticides having lapsed registrations.

Paraquat was registered in 1962 as a liquid SL20 formulation. In 1986, restrictions were imposed on the sale and use of this formulation by the Ministry of Agriculture, Forestry and Fisheries (MoAFF) due to issues with fatal poisoning [16] and a 4.3% paraquat ion/4.1% diquat ion combination product registered by ICI Japan.

Data for total pesticides sales were available for Japan from the literature for 1985–1999 [28] and from the FAO for 2000–2018. Between 1985 and 2000, total pesticide sales

Table 1. Registration status of OP and carbamate insecticides in Japan by WHO Hazard classes [26].

WHO Class	Registration Status	Number	OP insecticide name (registered year, lapsed year)	Number	Carbamate insecticide name (registered year, lapsed year)
Class Ia Extremely hazardous	Registered	0		0	
	Lapsed	4	EPN (1951, 2019), Ethoprophos (1993, 2002), Parathion (1952, 1969), Parathion-methyl (1952, 1969)	0	
	Never registered	9	Chlorethoxyfos, Chlormephos, Disulfoton, Mevinphos, Phorate, Phosphamidon, Sulfotep, Tebupirimfos, Terbufos	2	Aldicarb, Oxamyl
Class Ib Highly hazardous	Registered	3	Cadusafos (2000), Isoxathion (1972), Methidathion (1967)	1	Methomyl (1970)
	Lapsed	5	Dichlorvos (1957, 2012), Mecarbam (1960, 1987), Monocrotophos (1979, 2004), Thiometon (1960, 2002), Vamidothion (1963, 2002)	3	Butoxycarboxim (1979, 1988), Ethiofencarb (1982, 2007), Furathiocarb (1995, 2006)
	Never registered	16	Azinphos-ethyl, Azinphos-methyl, Bromophos-ethyl, Chlorfenvinphos, Coumaphos, Demeton-S-methyl, Dicrotophos, Edifenphos, Famphur, Fenamiphos, Heptenophos, Methamidophos, Omethoate, Oxydemeton-methyl, Propetamphos, Triazophos	5	Butocarboxim, Carbofuran, Formetanate, Methiocarb, Thiofanox
Class II Moderately hazardous	Registered	13	Acephate (1973), Chlorpyrifos (1971), Cyanophos (1966), Diazinon (1955), Dimethoate (1961), Fenitrothion (1961), Fenthion (1960), Phenthoate (1963), Phosalone (1965), Pirimiphos-methyl (1976), Profenofos (1986), Prothiofos (1975), Trichlorfon (1957)	8	Alanycarb (1993), Benfuracarb (1986), Carbaryl (1960), Carbosulfan (1983), Fenobucarb (1968), Fenothiocarb (1986), Isoprocarb (1966), Thiodicarb (1988)
	Lapsed	2	Ethion (1963, 2005), Pyridaphenthion (1973, 2009)	0	
	Never registered	11	Anilofos, Azamethiphos, Bromophos, Formothion, Methacrifos, Naled, Phosmet, Phoxim, Piperophos, Pyraclofos, Quinalphos	5	Bendiocarb, Metolcarb, Pirimicarb, XMC, Xylylcarb

Registration source: [24,25].

varied from 83,500 tons of active ingredients to 91,100 tons [28]. During these years, the amount of insecticide fell modestly (44,000 to 41,000 tons; 6.8% reduction) while herbicides fell less modestly (18,000 to 11,000 tons; 38.9% reduction) and fungicides increased markedly (21,000 to 40,000 tons; 90.5% increase) [28] (Figure 2). No data on sale of subclasses of insecticides or herbicides were available for this period. Between 2000 and 2018, there was a continuing fall in the use of insecticides (17,000 tons in 2018) and a small increase in use of herbicides (13,000 tons in 2018). OP insecticide sales fell markedly from 6000 tons in 2000 to 1500 tons in 2018 (75.0% reduction; Figure 2), while carbamate sales were low throughout this period.

Paraquat and diquat sales data were available from 1965. Paraquat sales increased to 1684 tons in 1982 (Figure 2(b)) before a rapid fall to 477 tons in 1986/1987 after registration of the lower concentration product. Sales thereafter fell further by 85% between 1987 (477 tons) and 2019 (74 tons). During the 1970s, diquat sales were typically 10–15% of paraquat sales. However, in 1986, diquat sales increased compared to paraquat sales, from 11% in 1985 to 158% in 1987 (Figure 2(b)). Sales thereafter have fallen steadily, from a peak of 756 tons in 1987 to 117 tons in 2019.

This fall in sales was associated with the Ministry of Health and Welfare and Ministry of Agriculture, Forestry and Fisheries requiring purchasers to show their identification card, and sign their name, when buying any paraquat product [29]. In addition, there has been an effort by agricultural technologists and farmers in Japan to replace paraquat products with the other herbicides due to its high toxicity

Deaths from pesticide poisoning

There were 221 deaths from pesticide poisoning in 2019, down from 2648 in 1986, a 92% reduction over 33 years (Figure 3). The class of pesticide was not reported by official statistics until 1979; from that year, deaths from "other pesticides" (ICD-9 989.4) exceeded deaths from OP and carbamate insecticides (ICD-9 989.3). In 1986, "other pesticides" (mostly paraquat [16]) were responsible for 2,188 (82.6%) deaths, while OP and carbamate insecticides were responsible for 460 (17.4%, Figure 3). By 2019, there was a greater

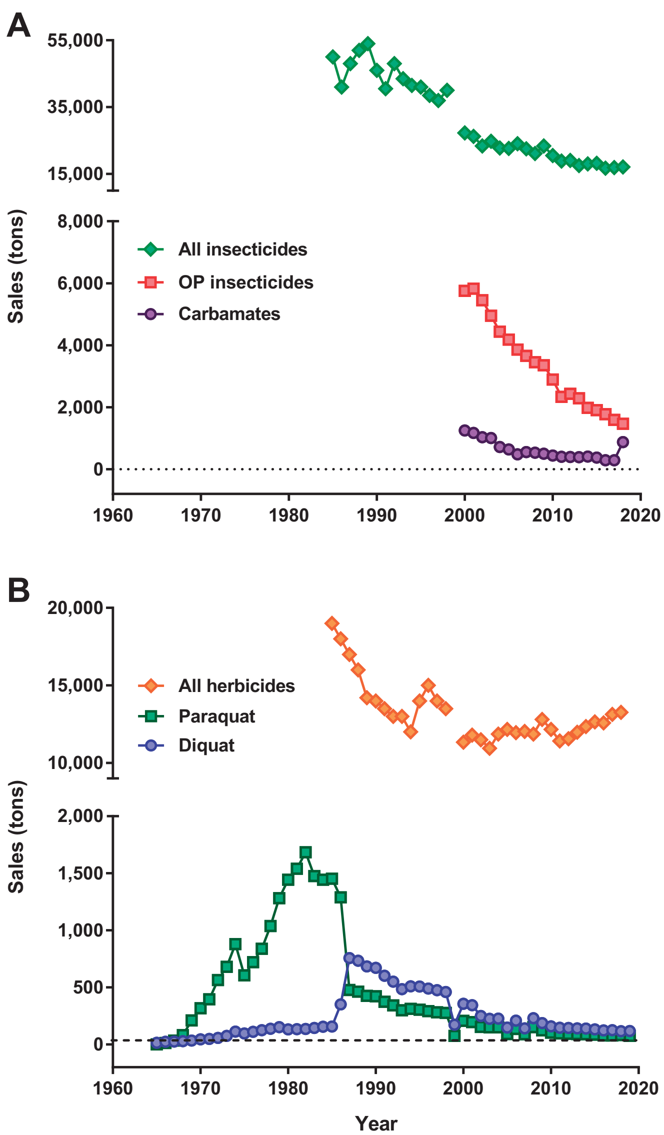

Figure 2. Use of (A) OP and carbamate insecticides from 2000 to 2018 and (B) paraquat and diquat herbicides in Japan from 1966 to 2019.

mix of pesticides responsible for deaths: herbicides and fungicides (86; 38.9%), OP and carbamate insecticides (68, 30.8%), and other pesticides (67, 30.3%).

The switch to the paraquat/diquat combination product was associated with a marked reduction in "other pesticide" deaths (from 2188 in 1986 to 1001 in 1990; 54.3% reduction). There was little change in number of OP and carbamate insecticide deaths during this period. However, since 1990, there has also been a steady decline in deaths from all classes of pesticide (Figure 3) associated with reduced sales of highly hazardous paraquat, diquat and OP insecticides (Figure 2).

Pesticides suicides made up a small and decreasing proportion of all suicides occurring in Japan. In 1985, when pesticide suicides were at their peak, there were 2038 (8.6%) recorded pesticide suicides out of a total of 23,627 suicides. In 2019, this had fallen to 146 (0.7%) of 20,094 suicides. Suicide was responsible for most pesticide deaths in both 1985 (2013/2476, 81.3%) and 2019 (146/221, 66.1%). Unintentional deaths also all fell by 83.8%, from 463 to 75, over this period.

Agricultural output

We looked at agricultural output using FAOStat data from 1995 to 2016 to examine a period when insecticide sales fell by 59.2% (OP insecticides by >50%), herbicide sales fell by 6.2%, and paraquat sales fell by 74.4%. Looking at a variety of crops including paddy rice, vegetables, and orchard fruits (Figure 4), we found no evidence of an effect of these reductions in pesticide use on agricultural output.

Relationship between pesticide sales and deaths

We finally examined the relationship between sales of the two key classes of pesticide and deaths from these pesticides, adjusted for year and unemployment rate. No evidence of association was found between the sale of diquat, paraquat, or combined and mortality rates by pesticide poisoning (1968–2019; Table 2(A)). When focusing on mortality rates by non-OP/carbamate pesticide poisoning (data available for 1979–2019; Table 2(B)), there was weak evidence for a positive association with the sale of paraquat ($b = 2.55$, 95% confidence interval [CI] − 0.32 to 5.42, $p = 0.080$) but not diquat ($b = -1.28$, 95% CI −5.72 to 3.16, $p = 0.56$). Graphic examination shows that when the restriction on paraquat use was introduced in 1986, this was accompanied by a marked reduction in paraquat sales and a downturn in non-OP/carbamate poisoning mortality rates from an upward trend to downward trend (Figure 5).

When focusing on data for more recent years (when detailed data for the use of herbicides and fungicides vs OP/carbamate insecticides were available), the annual changes in the use of herbicides and fungicides were associated with mortality by herbicides or fungicides (2000–2018; Table 2(C)); similarly, annual changes in the use of OP/carbamate insecticides were associated with mortality rates by OP/carbamate insecticides poisoning (2001–2018; Table 2(D)). Every one kiloton increase in the use of herbicides and fungicides was associated with an increase of 0.06 (95% CI 0.03–0.10; $p = 0.002$) deaths by herbicides or fungicides poisoning per 1,000,000. Every one kiloton increase in the use of OP/carbamate insecticides was associated with a rise of 0.21 (95% CI 0.08–0.35; $p = 0.003$) deaths by OP/carbamate insecticides poisoning per 1,000,000.

Discussion

This analysis of pesticide sales, poisoning and deaths, and of agricultural output, in Japan showed a marked reduction in sales of both paraquat and diquat herbicides and OP/carbamate insecticides that was associated with a 92% reduction in pesticide deaths but no change in agricultural output. Most deaths since the late 1970s were from herbicides and fungicides, in particular paraquat [6,16]. By 2019, the annual number of pesticides deaths had reduced from 2648 in 1986 to 221.

Regulations enacted in 1986 to reduce the concentration of paraquat ion in the standard formulation (20%) to 4.3% (with 4.1% diquation) was effective in reducing herbicide

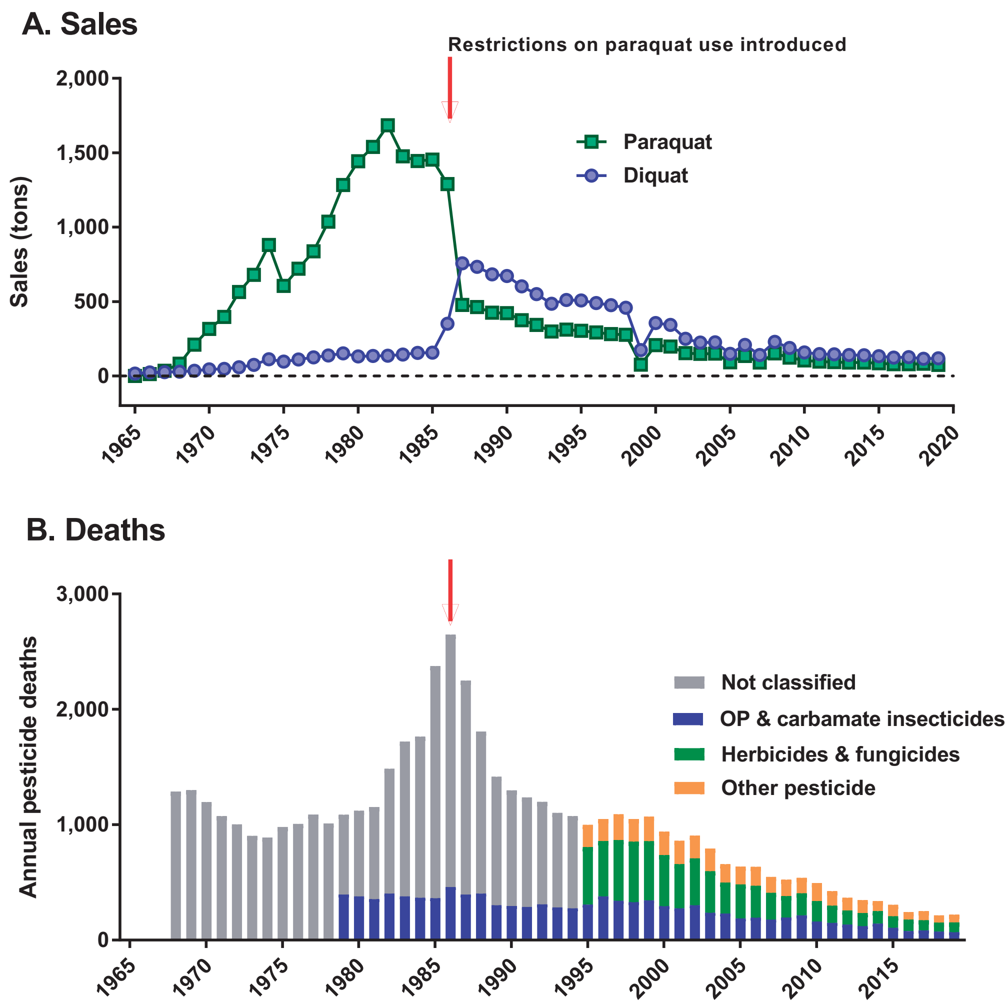

Figure 3. Deaths from pesticides in Japan 1968 to 2019. Source: Vital Statistics of Japan [26].

and fungicide deaths by 54% over the following five years. However, reduced sales of highly hazardous paraquat, diquat, and OP pesticides appears to be responsible for the subsequent steady reduction of all pesticide deaths from 1297 in 1990 to 221 in 2019.

The amount of OP and carbamate insecticides being used in Japan has fallen markedly over the last two decades, associated with the reduction in OP and carbamate deaths. No WHO Hazard Class Ia pesticides are now registered in Japan while only four Class Ib highly hazardous OP and carbamate pesticides are registered (cadusafos, isoxathion, methidathion, methomyl). Fatal poisoning cases have been recorded with the last three of these insecticides [14,30–32]. Twelve Class Ia/Ib insecticides have been withdrawn from the market (in particular, the key HHPs parathion and methyl parathion in 1969 and monocrotophos in 2004), likely explaining the paucity of deaths from OP insecticide poisoning relative to other Asian countries [2,33]. Deaths from OP and carbamate poisoning have been less common than deaths from paraquat since at least 1978 [16].

Japan is one of the few countries that uses a 4.3% paraquat ion/4.1% diquat ion combination product. We previously studied the case fatality of this product and noted a modestly lower case fatality than paraquat SL20 products (65% vs 75%) [7,17]. Ingestion of ≥50 mL of 4.3% paraquat ion/4.1% diquat ion usually resulted in a fatal outcome. The minimal lethal dose in humans is believed to be around 50 mg/kg, or 1–2 g (10–20 mL of the 20% product) [34]; the lethal dose of a 5% product would therefore be about 40–80 mL if the diquat did not contribute to toxicity. Since diquat is toxic [35], the lethal dose is likely to lie somewhere between these ranges, consistent with a dose of 50 mL being frequently lethal.

Other data suggest that dilution of paraquat products may be modestly effective at reducing deaths. Unpublished data from Japan in 1986–1987 reports a case fatality of 14/22 (63.6%) for the paraquat/diquat product versus 24/30 (80.0%) for paraquat SL20 products [36], a difference of 16.4%. In Sri Lanka, introduction of a reduced concentration paraquat SL product (6.5% ion) was associated with a reduction in mortality from 50% (for 20% ion products) to 23% [37]. These data highlight the potential for reformulation to contribute to reducing case fatality for self-poisoning, as occurred in India with replacement of high concentration 56% aluminium phosphide 3 g tablets by lower concentration powder formulations [38–40].

A wide variety of therapies and treatments have been studied in the last several decades for paraquat poisoning, but none have been effective in decreasing case fatality [41,42]. ICU techniques have improved over the last 50 years. However, this is unlikely to explain the reduction in deaths

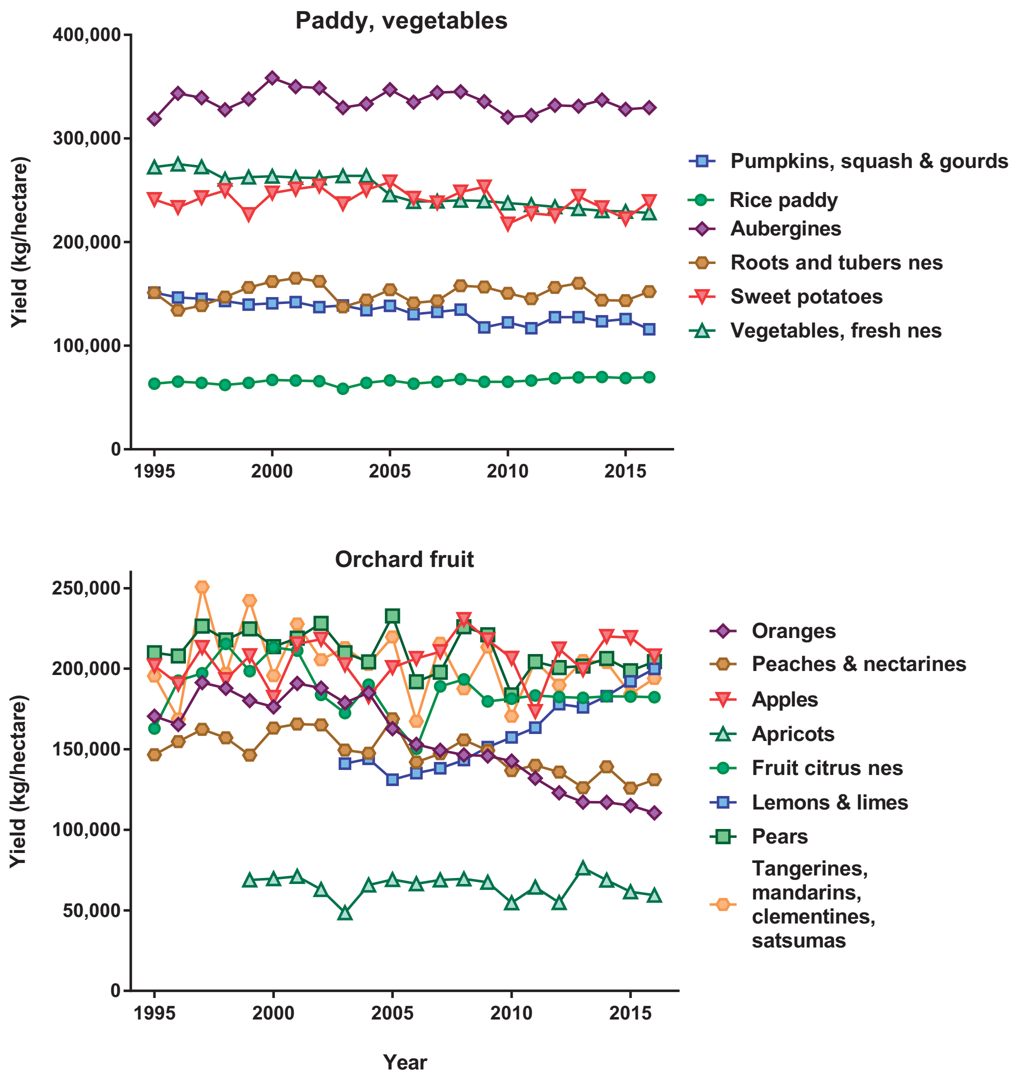

Figure 4. Agricultural output in Japan from 1995 to 2016 for selected paddy, vegetable and orchard crops (source FAOStat; http://www.fao.org/faostat/en/#data/QC).

Table 2. Prais-Winsten regression analyses of the associations between pesticide sale or use (kiloton) and mortality rate per 1,000,000 in Japan.

	b	(95% CI)	*p*
(A) Mortality rates by pesticide poisoning (1968–2019)			
Paraquat and diquat sale	1.63	(−0.77, 4.03)	0.18
Diquat sale	−1.48	(−5.81, 2.85)	0.50
Paraquat sale	1.92	(−0.42, 4.27)	0.11
(B) Mortality rates by non-OP/carbamate pesticide poisoning (1979–2019)			
Paraquat and diquat sale	2.51	(−0.76, 5.79)	0.13
Diquat sale	−1.28	(−5.72, 3.16)	0.56
Paraquat sale	2.55	(−0.32, 5.42)	0.080
(C) Mortality rates by herbicides or fungicides poisoning (2000–2018)			
Herbicides and fungicides use	**0.06**	**(0.03, 0.10)**	**0.002**
(D) Mortality rates by OP/carbamate insecticides poisoning (2001–2018)			
OP/carbamate insecticides use	**0.21**	**(0.08, 0.35)**	**0.003**

Note. Models were controlled for year and unemployment rate. CI: confidence interval. 95% CIs that do not include zero for *b* are highlighted in bold.

for either paraquat or OP insecticides. For paraquat, few patients are admitted to intensive care, due to futility. For OP insecticides, many of the most toxic pesticides kill patients soon after ingestion, before admission to hospital. The outcome for paraquat poisoning continues to be dependent on the paraquat ion dose absorbed and blood concentration [43,44]. In the absence of any effective antidote, paraquat's LD50 of about 50 mg/kg in humans [34,45] indicates that it should be categorized as a WHO Hazard Class Ib highly hazardous pesticide [25,46].

We also noted a marked fall in unintentional deaths, which would have included all occupational deaths, over this period. There has been little advance in occupational protection during this period. The use of personal protective equipment by farmers has increased – not only must they wear PVC gloves and rubber boots, but also a Goretex raincoat and a respiratory

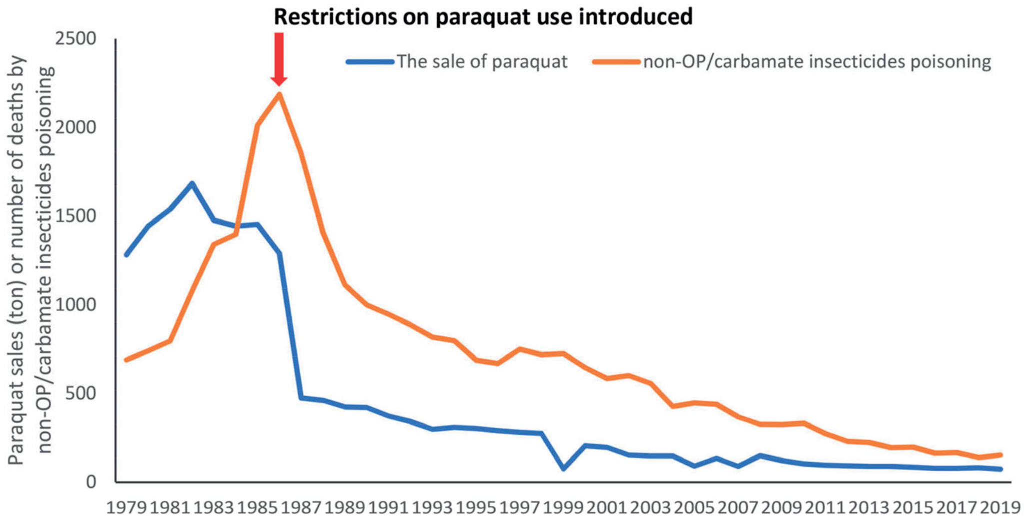

Figure 5. Trends in the sale of paraquat and number of deaths by non-OP/carbamate insecticides poisoning in Japan, 1979–2019.

mask for people directly using the pesticides. However, the main factor decreasing deaths from occupational pesticide poisoning is that pesticide manufacturers refrained from selling WHO class I hazardous pesticides according to the advice of the Ministry of Agriculture, Forestry and Fisheries.

A broad range of less hazardous pesticides ($n = 529$) are now registered in Japan. Recent reports of pesticide poisoning indicate that many cases now follow ingestion of the herbicides glyphosate [47] and glufosinate [48] and the insecticides fenitrothion [49,50] and imidacloprid [51]. These pesticides are of WHO hazard classes II and III, with lower case fatality than paraquat or Class I OP insecticides.

Reduced use of highly hazardous pesticides in Japan has not been associated with any consistent reduction in agricultural output. This provides yet more evidence that highly hazardous pesticides can be removed from agricultural practice without agricultural harm because effective chemical and non-chemical alternatives are available and affordable to farmers [52,53].

Limitations

The Japanese vital statistics system [26], and the international ICD-9 [54] and ICD-10 [55] system upon which it has been based since 1978, are not well set up for providing data on deaths from pesticide poisoning. Up until 1979, pesticide deaths were classified into a single category (T60) in the Vital Statistics of Japan. From 1979 to 1994, they were classified into just two categories – due to OP or carbamates insecticides (T60.0), or "other pesticides". Clinical observations indicated that the vast majority of deaths reported as being due to "other pesticides" were due to paraquat [16,22]. From 1995 onwards, with the introduction of ICD-10, deaths from pesticide poisoning were further divided into OP and carbamate insecticides (T60.0), herbicides or fungicides (T60.3), and other pesticides (T60.2). We have previously shown that most pesticide deaths, not just herbicide and fungicide deaths, were still due to paraquat during this period [7,17]. It is not yet clear whether ICD-11 will allow a better classification of pesticide poisoning, with sub-classification down to important individual compounds.

We were unable to obtain data on hospital presentations and admissions with pesticide poisoning in Japan which would have allowed us to compare how the reduction in death related to changes in case number and/or case fatality. Such data do not appear to be collected in Japan.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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