Paraquat in Developing Countries

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The herbicide paraquat is considered safe by industry and the bulk of regulators worldwide. However, determinants of exposure from 30 years ago persist in developing countries. Little is known about systemic absorption from occupational exposures. The relationships between exposure determinants, levels of external exposure, biomarkers of exposure, and outcomes are not clear. High rates of severe acute poisonings have been documented. In addition, topical injuries occur in as many as 50% of exposed workers. Non-worker populations are also at risk, particularly children. Long-term and delayed health effects include Parkinson's disease, lung effects, and skin cancer. Regulatory agencies have not fully recognized either the inherent toxicity of paraquat or the particular risks derived from exposures in developing countries. Independent risk assessment in the developing-country context and application of the precautionary principle are necessary to prevent adverse effects of dangerous pesticides in susceptible populations.
Key words: paraquat; herbicides; developing countries; international policy; occupational injuries; poisonings.

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The contact herbicide paraquat (1,1'-dimethyl-4,4'-bipyridylium dichloride) disrupts photosynthesis processes in plants. Paraquat is used in over 120 countries, commonly sold as Gramoxone®, a 20% solution. It is currently the third best-selling pesticide globally, produced by one of the world's largest agrochemical companies, currently named Syngenta (<www.syngenta.com/en/customer, July 2001>). Paraquat is labor-saving and cheap, and therefore especially popular and accessible to farmers in developing countries.

The use of paraquat has been questioned and discussed for decades in international and national regulatory bodies, nongovernmental organizations (NGOs), and scientific fora.[1–13] Reasons for alarm were frequent suicides, unintentional poisonings in children and adults, and skin and eye injuries. In the late 1980s, manufacturers added a blue pigment, a stenching compound, and an emetic substance to the formulation to make severe unintentional poisonings due to oral intake virtually impossible.[14] Industry has repeatedly claimed that paraquat has an excellent occupational safety record, when labeled instructions are followed.[14-17] In response to a report of a high frequency of suicidal paraquat poisonings in Trinidad,[18] the manufacturer recently stated that paraquat suicides are decreasing, and that safe use practices and training have decreased if not eliminated unintentional poisonings. They claim that "banning paraquat could add to the social distress associated with high suicide rates among subsistence farmers, by banning an essential tool to feed their families and enhance their prosperities."[17]

Paraquat has been banned or restricted in a number of countries. The U.S. Environmental Protection Agency (EPA) allows its purchase and use solely by certified applicators.[19] Paraquat is prohibited in Sweden, Finland, and Austria based on its acute toxicity and the absence of an antidote. In Norway, the manufacturers voluntarily canceled its registration.[20] In Germany and in The Netherlands, paraquat was banned because of its persistence in soil. The ban was subsequently lifted.[21] Paraquat is being reviewed in the European Union and is in use in ten of the 15 EU member states (<http://europa.eu.int>, status of current authorizations in December 2000).

In developing countries, where health hazards of pesticides are pronounced, paraquat is minimally restricted. In Indonesia, its use is restricted to large estates and certified applicators.[22] In April 2001, the government of Chile prohibited aerial applications (<http://www.sag.gob.cl>). In September 2000, the Central American Ministers of Health signed an agreement restricting the use of the most toxic pesticides, including paraquat.[23] The agreement has not been implemented yet.

The recommendation for classification by acute hazard of the World Health Organization's International Program on Chemical Safety (IPCS), followed by most developing countries, endorses a laissez-faire approach for paraquat by classifying it as a moderately

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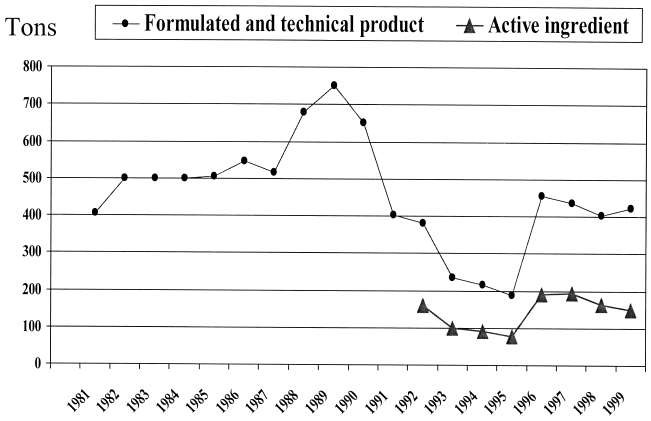

Figure 1—Tons of paraquat imported in Costa Rica: formulated and technical-grade solution between 1981 and 1999; active ingredient between 1992 and 1999.

toxic Class II pesticide, based on oral toxicity in rats.[24] Paraquat was initially considered by the Prior Informed Consent (PIC) Expert Group for inclusion in the list of PIC pesticides of the FAO Code of Conduct, as a pesticide posing special problems in developing countries. Heavy industry lobbying, however, has kept paraquat excluded from the PIC list. The PIC Expert Group suggested during the 1992 FAO/UNEP joint meeting on PIC in Rome, that "FAO consult with PAHO regarding the reported accidents, deaths and incidents in Latin America and consider a consultancy involving visits to five or six countries to investigate the reports of incidents and provide a report on the actual conditions of use." This consultancy never took place. In 1995, discussions of the PIC Convention stopped any further actions (Barbara Dinham, personal communication). The World Bank agreed to consider not recommending paraquat in World Bank projects,[9] but never implemented this policy.

Deficient working conditions, improper maintenance, climatic conditions, illiteracy, and general poverty make controlled and safe use of paraquat extremely difficult in developing countries. This article reviews data on use, human exposure, toxicity, and health effects of paraquat, focusing on Costa Rica, Central America, and other developing countries, to provide an overview of basic data for risk assessment and decision making in developing countries.

USE OF PARAQUAT AND HUMAN EXPOSURE

Use in Central America

Paraquat has for decades stayed among the pesticides imported by highest volume in Central American countries: Belize, Costa Rica, El Salvador, Guatemala, Honduras, Nicaragua, and Panama.[23,25] It is used for weed control on bananas, coffee, plantain, sugarcane, corn, palm hearts, ornamentals, trees, citrus fruits, oil palms, macadamias, mangoes, avocados, and other crops; as a pre-emergent herbicide on crops or for the cleaning of land; as a defoliant on cotton; for destruction of potato stems and tops; as a post-harvest desiccant on pineapple plants; in roadside weed control; and around buildings and homes, especially in rural areas (database IRET-UNA). Paraquat became widespread in the late 1970s. By the end of the 1980s, technical-grade paraquat was processed in pesticide-formulating factories in the seven Central American countries.[25] Because it is a contact herbicide, spraying of paraquat occurs with high frequency, especially under humid weather conditions with rapid plant growth, for example, every six to eight weeks on banana plantations. Import figures, available for Costa Rica from 1981 (database IRET-UNA), peaked at 750 tons in 1989, followed by a steep decline to 187 tons in 1995. The decrease was related to substitution for it by less toxic herbicides, such as glyphosate. This occurred on the banana plantations in particular, under consumer pressure from abroad, since paraquat could no longer be used for bananas with an eco-label. At present, the use of paraquat is on the rise again, due to increased use for other crops such as pineapple, with over 420 tons having been imported in 1999 in Costa Rica (Figure 1). No Central American country restricts the agricultural use of paraquat in any manner, with the exception that it is not registered for aerial applications.

Occupational Exposure

Exposure to paraquat occurs by dermal and ocular contact, by inhalation, or by oral intake. Early occupational exposure studies in Sri Lanka, Malaysia, and the United States assessed exposure levels of knapsack and field tractor applicators[26-29] and occupational exposures for aerial applications.[30] More recently, exposure-assessment studies of knapsack applicators have also been performed in Sri Lanka[31] and Costa Rica.[32,33] Table 1 gives an overview of the studies performed. The studies measured dermal, inhalation and/or urinary paraquat levels of applicators and/or plantation workers. In general, dermal exposure levels seemed most important, whereas measured inhalation levels were relatively low. Four of six studies assessing uptake found paraquat in urine at the end of one or more working days. However, the relationships between exposure determinants, levels of external exposure, and levels in urine were far from clear and not investigated with much detail.

Measured exposure levels and exposure circumstances among backpack sprayers seemed quite comparable in the different studies, with the exception of the remarkably lower levels observed in a study in the United States.[27] Nevertheless, the interpretations of similar findings of studies performed in several tropical countries differed considerably. The studies carried out by or in collaboration with Imperial Chemical Indus-

tries (currently Syngenta) concluded that paraquat is most unlikely to cause serious health problems under correct conditions of use,[15,26,28,31] despite the fact that in several of these studies between 40% and 50% of the workers had experienced topical injuries.[26,34] Other researchers concluded that, even when measured levels were unlikely to result in acute or chronic health effects, spray operators were continuously at risk for high exposures that might lead to severe intoxication and injuries. Even on plantations where serious efforts had been made to reduce risks, dangerous situations and events of inadequate handling were registered.[32,33]

Dermal Exposure

Dermal exposure was the most likely route of uptake in studies that reported paraquat in urine (see Table 1). Paraquat is poorly absorbed through intact skin, but penetration is considerably increased by damage to the skin, which is of particular concern because paraquat itself is a skin irritant.[35] Total dermal exposure levels in the studies presented in Table 1 were assessed by residue analysis on pads and coveralls or from hand washing, with calculations in mg/h or mg/kg of applied paraquat of actual or potential dermal exposure. It is noteworthy that the existing exposure data have only limited value for risk assessment; however, they give insight into possible exposure routes and mechanisms. Conceptual models of dermal exposures and new methods for assessing dermal exposure have only recently been developed and underlying mechanisms of exposure scrutinized scientifically.[36]

On banana plantations, dermal exposures varied due to differences between plantations rather than differences between applicators or between days.[32,33] The body parts identified as having the highest levels of exposure were hands, wrists, back, and scrotum. Mechanisms of exposure included splashing during preparation of the spray solution and open transportation, deposition of spraying mist, contact with spray solution when filling knapsacks, leaking of knapsacks on back and groin regions, adjustment of spray equipment, and walking through sprayed vegetation.

Use of protective clothing is supposed to considerably reduce dermal exposure. However, few studies have evaluated the effectiveness of personal protection or other safety measures.[33,37] Swan compared the exposure of applicators using normal clothing with exposure levels of workers using gloves, boots, and respiratory protectors.[26] Fewer positive urine samples were identified in workers using protective equipment (7–14% versus 18–50%) and fewer skin complaints were reported. Spruit and van Puijvelde[33] performed a small study to evaluate the use of protective equipment at four banana plantations by means of fluorescent tracer and cotton gauze. All workers (n = 8) had received training in the safe use of protective equipment. Wearing jeans and an apron on the back seemed to reduce exposure considerably. Dermal exposure levels were lower than those measured by van Wendel de Joode et al. (1996)[32] (see Table 1). Exposures occurred especially in body areas involved in movements (knees, elbow, wrists) and those becoming wet by transpiration or pressure from belts of the knapsack (armpits and shoulder region). Despite the use of gloves, the workers' hands remained exposed due to cross contamination by taking the gloves off and putting them on. Occlusion of pesticides by protective devices may result in increased absorption.[38,39]

Inhalation

In general, inhalation exposure is not considered a relevant exposure route, due to the low volatility of paraquat and the droplets' being too large to enter the small airways during application.[19] Ambient air concentrations are generally well below NIOSH and OSHA limits (0.1 mg/m^3 and 0.5 mg/m^3 TWA, respectively) (see Table 1). However, van Wendel de Joode et al. could not exclude that inhalation was relevant for internal exposure.[32] Inhalation exposures measured in this study appeared to be strongly influenced by differences between days, which could be due to variable wind speeds and other weather-related conditions. In Costa Rica, the use of motor driven backpacks to spray paraquat is not uncommon. These may increase the fraction of respirable particles.[26] It has also been put forward that the respirable fraction of paraquat may become larger under certain climatic conditions.[40] Several studies suggest that inhalation may play a role in systemic paraquat absorption.[12,40,41]

The low inhalation levels measured in the different studies seem inconsistent with the frequent episodes of epistaxis, or nosebleeds, reported among exposed workers,[3,15,26,32,42,43] which are due to local irritation of the upper respiratory tract by paraquat particles.[19] It is possible that inhalation exposure levels are incidentally higher than those reported in the studies of Table 1, since none of the studies with assessment of inhalation exposures mentioned the occurrence of epistaxis during the measurements. However, it remains unclear at which inhalation-exposure levels epistaxis occurs and whether these levels may be relevant for systemic uptake.

Oral Exposure

Oral exposure may occur during work when ingesting paraquat solution by mistake, through splashes in the mouth during mixing and transporting, by eating with contaminated hands, by blowing or sucking spray nozzles, or when eating contaminated food.[12,15,28,32,44] In addition, oral ingestion may occur as a result of swallowing the "run off" on the face caused by droplets when the operator is working in the spray mist.[15] Reten-

TABLE 1. Dermal, inhalation, and Urinary Paraquat Levels of Workers Exposed to Paraquat

Reference	Country	Crop	Type of Application	Total Dermal Exposure	Inhalation Exposure	Paraquat in Urine (mg/L)	Spray Solution (w/w%)
Spruyt and van Puijvelde, 1998[33]	Costa Rica	Banana	Mixing, loading, backpack spraying	0.12–10.5 mg/h* 2.6–210 mg/kg §*	Not assessed	Not assessed	0.10–0.20
van Wendel de Joode et al., 1996[32]	Costa Rica	Banana	Mixing, loading, backpack spraying	2–57 mg/h* 35–1,130 mg/kg §*	< 0.1–24 µg/m3	< 0.03–0.24	0.10–0.20
Chester et al., 1993[31]	Sri Lanka	Tea	Mixing, loading, backpack spraying	40–600 mg/kg §,† 830–4,580 mg/kg §,†	Not assessed	< 0.03	0.03–0.04
Chester and Ward, 1984[30]	United States, California	Cotton	Aerial spraying				
			Mixer/loader	0.18–0.20 mg/h*	0.1 µg/m^3	Not assessed	0.29
			Flagger	0.10–2.39 mg/h*	< 0.10–26.3 µg/m^3		
			Pilot	0.05–0.26 mg/h*	< 0.10–0.34 µg/m^3		
Wojeck, 1983[29]	United States, Florida	Tomatoes	Boom application				
			Open tractor	168.59 (±81.85)¶ mg/h†	70 (±40) µg/h	< 0.012	0.05
			Enclosed cab tractor	26.91 ± 25.63 mg/h†	10 (±10) µg/h		0.05
			High clearance tractor	18.38 (±13.58) mg/h†	20 (±10) µg/h		0.07
		Citrus	Boom application				
			Open tractor	28.50 (± 8.31) mg/h†	10 (±10) µg/h	<0.012-0.033	0.11
			Open tractor	12.16 (±4.69) mg/h†	0 (±0) µg/h		0.07
Chester and Woolen, 1981[28]	Malaysia	Rubber, oil palm	Backpack spraying	<0.1–12.4 mg/h* 12.1–169.8 mg/h†	< 0.01–11.17 µg/h < 0.05–93.12 µg/m^3	< 0.05–0.69	0.1–0.2
Staiff et al., 1975[27]	United States	Orchards Garden	Backpack spraying Pressurized dispenser	0.01–3.40 mg/h* 0.01–0.57 mg/h *,‡	< 1–2 µg/h < 1 µg/ h	< 0.02	0.2
Swan, 1969[26]	Malaysia	Rubber	Backpack spraying	Not assessed	Not assessed	< 0.01–0.32	0.25

*Actual dermal exposure: exposure of covered and uncovered skin.
†Potential dermal exposure: exposure on clothing and uncovered skin.
‡Measured according to WHO standard protocol (1975).
§Milligrams per kilogram paraquat handled or sprayed.
¶Standard error of the mean.

tion of paraquat particles in the nose and mouth, as evidenced by sore throat and nosebleed, may contribute to the internal dose through swallowing.[12]

Non-occupational Exposure: Risk for Children

The border between occupational and non-occupational accidental exposures is not always easy to distinguish. Accidental oral exposure may occur under a variety of circumstances. Confusion of paraquat concentrate or solution due to inappropriate storage in refreshment or liquor bottles has apparently diminished but still occurs. Accidental intake at home is in Costa Rica often associated with alcohol intake.[45]

Children's exposures are of special concern. To determine oral exposure of children from containers for garden use, a US EPA study analyzed paraquat residues of diluted spray on nozzles and nozzle discharge. Based on a LD_{50} for rats of 100 mg/kg, the maximum observed value for oral exposure would represent 0.14% of the toxic dose for a child of 12.3 kg. The authors concluded that despite the ample safety margin there is a potential hazard, in particular because of greater toxicity in humans than in rats.[27] In Costa Rica, between 1991 and 1995, the exposure circumstances of severe and fatal poisoning in children aged 1–6 included the cases of two toddlers placing respectively a rinsed spray jet and a bottle top into their mouths, two cases of confusion of bottles stored in the kitchen, two cases of children playing with empty bottles, and a 7-year-old girl giving "cough medicine" to a younger brother.[45]

TOXICITY DATA AND HEALTH EFFECTS

Acute Systemic Toxicity

Systemic paraquat poisoning is characterized by burns of the upper digestive tract when ingested, as well as by multi-organ failure, including the lungs as the main target organ and the liver, kidneys, and, less frequently, the central nervous system, heart, suprarenal glands, and muscles. In fatal cases, depending on the dose, death is due to respiratory failure from pulmonary edema within a few days or from pulmonary fibrosis up to over a month after the poisoning event. No antidote or effective treatment is known.[11,43]

Toxicity data from animal bioassays used by regulatory agencies are not fully consistent. The U.S. EPA classifies the acute toxicity of paraquat due to oral intake as Category II, moderately toxic, based on the LD_{50}s of 283 and 344 mg/kg in female and male rats, [19] while WHO-IPCS uses an LD_{50} of 150 in rats as the basis for its classification.[24] Acute oral toxicity is much higher in other mammals, for example guinea pigs (22–30 mg/kg), monkeys (50 mg/kg), cats (40–50 mg/kg), and dogs (25–50 mg/kg).[43,46] For humans, the lowest fatal dose recorded is 17 mg/kg.[43] Still lower doses may be fatal, especially in children.[12,47]

The EPA classifies systemic toxicity of paraquat from dermal absorption as slightly toxic, category III, based on LD_{50} > 2,000 mg/kg (no observed mortality dosing rats during 24 hours with 2,000 mg/kg).[19] In other animal bioassays, the dermal toxicity of paraquat has been reported to be much higher, with LD_{50}s of 80 and 90 mg/kg in male and female rats,[43] and 236–500 mg/kg in the rabbit.[43,46] In addition, paraquat is caustic and may, by increased dermal absorption, originate systemic poisonings.[7,35,48]

The U.S. EPA classifies acute toxicity by inhalation as Category I, highly toxic based on an inhalation LC_{50} of the respirable fraction of paraquat of 1 μg/L. However, since agricultural formulations of paraquat contain few respirable particles and paraquat's volatility is low as discussed above, the EPA does not consider respiratory toxicity a toxicologic endpoint of concern for systemic paraquat absorption and does not consider it in its risk assessment.[19] Systemic toxicity after respiratory exposures has, however, been reported.[12,40,41]

Epidemiology of Severe and Fatal Paraquat Poisonings

Thousands of paraquat poisonings and fatalities have been reported in case reports, case series, and surveys, and through surveillance systems, in particular in developing countries. Table 2 illustrates incidence and mortality data for paraquat poisoning in selected countries, including epidemics with very high fatality rates in Asia and Latin America, including Malaysia, Fiji, Japan, Sri Lanka, Surinam, Mexico, Costa Rica, Trinidad y Tobago, and Samoa.[49-59] Incidence and mortality rates vary enormously according to patterns of paraquat use, prevention and control programs, types of registers, and reporting practices. Despite likely underreporting, in some developing countries[45,52,58,59] the rates were between ten- and 300-fold those reported in the United States, the United Kingdom, Ireland, or Finland.[5,59-62] Recent figures available for Central America and the Pacific Islands are similar in magnitude to those in many countries in the 1980s. Despite precautionary measures, the incidence of fatal paraquat poisonings, particularly suicides, increased in Costa Rica during 1992–1998 as compared with the period 1980–1986.[45] Reports of severe unintentional poisonings and suicides have continued to appear also from many other countries.[63-71]

The surveys in Table 2 refer mainly to suicidal poisonings, but many include also cases of unintentional paraquat poisoning. The annual incidence rate of severe hospitalized paraquat poisonings in Costa Rica is estimated at 44 per million inhabitants, and the incidence of fatal paraquat poisonings at 15 per million during 1980–1986. Seventy five percent were accidental and occupational poisonings. Forty-eight percent of

TABLE 1. Numbers and Incidence Rates of Paraquat Poisonings in Selected Countries

Country (Reference)	Time Period	Type of Register	Poisonings			Average Annual	
			Total No.	Fatalities No.	Fatality Rate %	Incidence (per Million Inhabitants)	Mortality (per Million Inhabitants)
Perak, Malaysia[49]	1980-1982[a]	Hospitalizations	94	61	65	46	31
Fiji[50]	1983	Hospitalizations	59	34	58	90	51
United States[5]	1984	Poison control centers	153	1	0.6	0.7	0.004
United Kingdom[5]	1980-1984	Poison control centers	931	190	20	16	0.7
Ireland[5]	1982-1984	Poison control centers	166	30	18	16	3
Japan[51]	1985	Hospitalizations		>1,900			16
Surinam[54]	1985-1986	Hospitalizations	82	58	71	140	81
Finland[63]	1980-1982/ 1987-1988	Hospitalizations	5	0	0	1	0
Sri Lanka, 3 districts[53]	1986	Hospitalizations	171	84	49	43[b]	21[b]
Sri Lanka, Galle district[52]	1986	Hospitalizations + fatalities	151	103	68	170	116
England, Wales[60]	1981	Fatalities		55			1
England, Wales[60]	1989	Fatalities		13			0.3
England, Wales[61]	1990-1991	Fatalities		33			0.6
Mexico, Chiapas[55]	1988-1990	Hospitalizations + fatalities	25	16	64	31	20
Trinidad y Tobago, Southern part[57]	1996	Fatal suicides		39			8
Samoa, Pacific Islands[58,59]	1979-2000	Fatal suicides		363			>100
El Salvador (Unit of Epidemiology, Ministry of Health)	1998-2000	Surveillance system	923	94	10	49	5
Nicaragua (Program of Toxic Substances, Ministry of Health)	1999-2000	Surveillance system	570			52	
Costa Rica (26 hospitals and FMDc)[56]	1980-1986	Hospitalizations + fatalities	749[d]	257[e]	34	44	15
Costa Rica (2 rural and 4 reference hospitals and FMDc)[45]	1992-1998	Hospitalizations + fatalities	550[f]	355[g]	48[h]	22	14
Costa Rica, San Carlos (coffee / grains)[45]	1992-1998	Hospitalizations	116	48	41	119	42
Costa Rica, Guápiles (banana, ornamental plants)[45]	1992-1998	Hospitalizations	169	74	44	201	88

[a]Observation period of 18 months.
[b]Estimate based on population figure for 1994.
[c]FMD: Forensic Medical Department.
[d]Figure includes 516 hospitalized paraquat poisonings from 2,294 reviewed hospital files, plus an estimated 23% of the 1,036 hospitalizations without review of medical file.
[e]Based on data from Wesseling et al., 1993. Figure includes 169 fatalities with autopsy at FMD and a 52% increase observed after combining fatalities from hospital files with FMD data.[55]
[f]Figure includes 376 severe hospitalized paraquat poisonings in 2 rural and 4 reference hospitals in San José and 174 fatalities at the FMD from other non-reviewed hospitals.
[g]Number of fatal paraquat poisonings combining data from overlapping cases in the reviewed hospital and autopsy files at FMD.
[h]Based on the observed 181 fatalities among 376 hospitalizations.

the paraquat fatalities with identified causes were unintentional, mostly after accidental ingestion but also after occupational exposures.[12,56,72] Severe paraquat poisonings and fatalities in children have been reported,[5,12,47,56,72-77] ranging from accidents with extremely low doses[12,47,72] up to homicides.[76,77]

Although by far the majority of paraquat poisonings occur by oral intake, a number of reports of severe and fatal occupational and accidental poisonings after skin absorption are available.[78-89] One report concerned an unintended death following vaginal absorption.[90] It has been alleged that systemic effects do not occur at recommended dilution rates.[15,16] However, in 1983 there was a fatal case in which a farmer applied a paraquat solution diluted according label instructions (0.5% solution of paraquat) for 3.5 hours during which time skin exposure resulted from a leaking knapsack.[80] The farmer died within a week after application due to

TABLE 3. Surveys of Occupational Paraquat Injuries among Wage-earning Agricultural Workers in Costa Rica Reported to the National Insurance Institute (INS), 1982–1996

Geographic Area (Reference)	Time Period	Inquiries with Paraquat	Injuries with Other Herbicides	Injuries with Non-specified Herbicides	Total Paraquat Injuries*	Paraquat Injuries in One Month	Estimated Source Population	Incidence Rate per 1,000 in One Month
Entire country[96]	June 1982	25	1	38	62	62	129,523	0.5
Entire country (excluding San José)[56]	1986	173	25	346	475	40	115,908	0.3
Entire country[96]	June 1987	18	2	53	66	66	139,418	0.5
Entire country[96]	June 1992	44	5	42	82	82	129,101	0.6
Atlantic Region[96]	June 1982	21	1	18	38	38	14,895	2.6
Atlantic Region[96]	June 1987	15	0	23	38	38	19,735	1.9
Atlantic Region[96]	June 1992	28	2	26	52	52	24,243	2.2
Atlantic Region, Limón†[95]	Jan–June 1990	38	1	37	74	12	12,094	1.0
Atlantic Region, Guápiles†[95]	1988–1989	161	2	119	279	12	9,895	1.2
Guápiles, banana workers[97]	1993	80	7	76	150	12	13,206	0.9
Guápiles, banana workers[97]	1996	45	18	56	85	7	14,973	0.5
Guápiles, banana herbicide sprayers[97]	1993	71	6	76	141	12	440	26.7
Guápiles, banana herbicide sprayers[97]	1996	43	18	51	79	7	495	13.3

*Including nonspecified herbicides proportionally.
†Central American Institute for Studies on Toxic Substances, unpublished data.

paraquat-induced systemic intoxication. Wesseling et al. described 15 unintentional fatal paraquat poisonings, of which five were due to contact with diluted spray solution.[12]

Irritation of Skin and Eyes

The U.S. EPA concluded that paraquat causes moderate to severe eye irritation (Toxicity Category II) and minimal dermal irritation (Category IV), based on toxicity experiments in rabbits.[19] In fact, dermal lesions observed in workers range from mild irritation to blistering and ulceration (second- and third-degree chemical burns), often in the genital area.[3,43] Eye injuries may range from blepharitis and conjunctivitis to ulcerations or keratosis of the cornea; and nail damage due to prolonged hand contact with paraquat ranges from localized discoloration to temporary nail loss.[3,43]

Skin, nail, and eye lesions have been reported,[42,74,91-94] including some in children.[72,74,84] Workers in formulating factories were at high risk. A survey among 18 paraquat formulation workers in the United Kingdom found that 14 (78%) had experienced nail damage, nosebleed, blepharitis, or skin lesions with delayed healing. In Malaysia, 15 of 18 formulators presented with topical lesions, such as dermatitis or chemical burns (50%), and eye injury or blepharitis (39%).[42] Few data from epidemiologic studies or surveillance systems relative to topical injuries among agricultural workers are available. In California between 1971 and 1985, 231 paraquat-related cases of illness were reported, 38% being systemic poisonings and 62% topical injuries,[85] fewer than ten topical cases per year. However, skin burns and eye lesions from paraquat exposure are common among herbicide sprayers in developing countries, where no accurate statistics are available. In a number of the previously mentioned exposure-assessment studies, paraquat-related topical injuries were mentioned. In Malaysia, in one study approximately half of 24 applications and in another study 44% (12/27) of paraquat sprayers experienced skin or eye injuries during 14- and 12-week spraying periods, respectively.[26,34] In Costa Rica, three of 11 paraquat sprayers on banana plantations mentioned blistering of the skin on the hands, thighs, legs, back, and scrotum; two had experienced eye irritation; three, nail damage; three, epistaxis, and one, a burning sensation in the nose, during the preceding year.[32]

In Costa Rica, a number of surveys on occupational injuries among wage-earning workers were carried out by the Central American Institute for Studies on Toxic Substances between 1982 and 1996.[56,95-97] A summary of the results is presented in Table 3. In absolute numbers, hundreds of paraquat injuries occur each year in Costa Rica, most of them in the banana-producing Atlantic Region. The majority of victims (60%) presented with skin burns or dermatitis, and 26% had chemical eye injuries. The remaining 14% represented systemic poisonings, nosebleeds, and nail damage.[97] Incidence rates decreased over time, being the lowest

in 1996 (0.5 per 1,000 banana workers during a one-month period). Most of the injuries were concentrated among herbicide applicators, with monthly rates of 26.7 and 13.3 per 1,000 for 1993 and 1996, respectively.

Long-term and Delayed Health Effects

The California EPA acknowledges evidence of chronic effects from long-term exposures in the lung, liver, kidneys, and eyes in rats, dogs, and mice.[98] The U.S. EPA recognizes pulmonary effects and dermal lesions.[19] Paraquat does not appear to be mutagenic, but is weakly genotoxic.[19,98] Developmental and reproductive effects occur at doses higher than the maternal toxicity dose.[19,98] However, paraquat crosses the placenta. Fetal death in pregnant women poisoned by paraquat and neonatal death after induced delivery have been reported.[72,99,100] Neurotoxicity has not been evaluated by regulatory agencies. Animal bioassays[101,102] and clinical and pathologic scrutiny of human poisonings[103,104] revealed behavioral dysfunction and histologic changes in the brain. Paraquat has been linked with Parkinson's disease.[105,106] A synergistic mechanism with ethylene bisdithiocarbamate fungicides has been proposed.[107]

A number of studies failed to find lung damage in workers with prolonged exposures to paraquat in the United Kingdom,[42] Malaysia,[26,42,34] and Sri Lanka.[108] However, in several studies diagnostic tools, such as review of clinical records[42] and x-ray and clinical examinations,[26] were insensitive, or the exposures were much lower than in other occupational settings in developing countries.[108] Thus, a study in Nicaragua reported a dose–response gradient between intensity of exposure, as measured by history of skin lesions and the prevalence of respiratory symptoms.[109] In South Africa, clinical and histologic evidence of lung lesions was observed among exposed workers who had dermal injuries.[2] Arterial oxygen desaturation during exercise has been associated with long-term paraquat exposure.[110] This test was not used in the earlier non-positive studies.[34,108] Syngenta is now funding a US$677,000 project to evaluate long-term pulmonary effects among paraquat exposed workers in Costa Rica (<http//obgyn.net.ads>; Health & Medicine Week, May 14, 2001).

Carcinogenicity

The International Agency for Research on Cancer (IARC) has not evaluated paraquat for carcinogenicity. In the 1980s, the U.S. EPA concluded that there was some evidence of carcinogenic effects from paraquat based on a study in rats with excesses of adenomas and carcinomas in the lung, and squamous cell carcinomas in the forehead. Pathologists disagreed on how many of the proliferative lung lesions were neoplasias and, in the end, the lesions were considered secondary to chronic inflammatory processes.[98] Following a claim of industry that the tumors of the forehead appeared in various locations and could therefore not be considered a single entity, the statistically significant excesses disappeared after stratification, and the results were reinterpreted as negative.[19] The California EPA concluded that the tumors were not the result of oral intake of the powdered feed containing paraquat, but several members of the review committee felt that the tumors could have been the result of topical contact with the feed.[98] Based on various arguments, paraquat's Class C (limited evidence in animals and lack of data in humans) was downgraded to Class E (evidence of non-carcinogenicity in humans)[19] with no consideration of human evidence.

In Taiwan, squamous cell carcinoma of the skin, actinic keratosis, and solar lentigo have been associated with combined exposure to sunlight and paraquat among workers in 28 paraquat factories.[111] In Costa Rica, a geographic study found excesses of different skin cancers (lip cancer, penile cancer, non-melanomous skin cancer, and skin melanoma) in coffee-growing regions, as well as an excess of skin melanoma in men in the banana-producing Atlantic region,[112] both crops with extensive paraquat use. A cohort study among Costa Rican banana workers also found an increased risk for skin melanoma.[113]

RISK ASSESSMENT AND REGULATORY RECOMMENDATIONS

Decision-making processes in developing countries tend to be less transparent than those in industrialized countries. In Latin American countries, national regulatory authorities habitually assign compounds to acute toxicity categories according to the WHO-IPCS recommendations for hazard classification.[24] Other international bodies and agreements, such as FAO food tolerances and the Prior Informed Consent (PIC) of the FAO Code of Conduct are considered in registration.[114,115] Latin American countries are strongly influenced also by the U.S. EPA, although as a rule only in broad terms, "to ban or not to ban." Any pesticide forbidden, never registered, or with a voluntary cancellation by the manufacturer may still have food tolerances. The main driving regulatory restrictions for developing countries today are the food tolerances related to the agricultural exports.

The EPA toxicity classifications and risk-management decisions are of limited use in Latin America. First, the toxicity classifications assigned by the EPA as well as other major regulatory bodies are based on standard experimental testing protocols in strict laboratory conditions. Second, when assessing the risks, toxicity data are integrated with exposure data, collected under conditions of good agricultural practices that have little resemblance to the circumstances prevailing in devel-

oping countries. Available epidemiologic evidence of human health effects from outside the United States has been considered only marginally at best. Third, EPA restrictions are adopted south of the U.S. border only in cases of a total ban that includes food tolerances. This is not the case with paraquat. More subtle risk-assessment details, including a robust RUP (restricted-use pesticide) status of paraquat in the United States, are not incorporated into national legislations in the South. A considerable proportion of paraquat in Central America is imported from the US, without major warning about the restricted regulatory status.

Risk management of paraquat in the United States and elsewhere relies largely on safety instructions on the label. Adversities that are consequences of not complying with label instructions are not considered the manufacturer's responsibility. In developing countries, application of paraquat in accordance with correct procedures as indicated on the labels seems unrealistic, even in the presence of industry efforts to promote safe and effective use of paraquat by education and training.[22,116] A label may indicate many good agricultural practices, but the possibility of following these instructions in the field may be very small. In addition, the effectiveness of training programs performed by industry is not evaluated in proper terms of exposure, health effects, or risk reduction.[117] The key issue is that in Central America, and in most other developing regions as well, insights into the risks from exposure in the local context and the know how are lacking. Risk assessment concepts or strategies such as the precautionary principle are not applied when it comes to registering the use of a pesticide such as paraquat.

CONCLUSIONS AND FINAL REFLECTIONS

- Paraquat is one of the most widely used pesticides globally and in most countries it is used without restrictions. However, some countries have restricted its use.
- Relatively few exposure studies and hardly any intervention studies have been performed.
- Understanding of exposure determinants such as climatic circumstances, types of crops, or application methods is limited. It is clear, nonetheless, that paraquat often is applied under hazardous conditions and that in developing countries application techniques have not considerably improved during the last 30 years. Transport systems are still open systems, and application equipment easily fails, resulting in high-level exposures
- Possibilities to reduce exposures by the wearing of protective clothing seem limited. The effectiveness of control measures under tropical conditions remains largely unevaluated.
- Relatively few recent surveys of paraquat poisonings are available. It is uncertain whether this reflects a decline in the incidence of severe poisonings or waning of interest in the problem.
- Suicides increased in Costa Rica in the 1990s compared with the 1980s. Recent reports of high rates of suicides come also from other developing countries.
- Despite the incompleteness of available data and consequent difficulties of interpretation and comparison, paraquat still clearly represents a severe public health problem.
- Occupational and non-occupational hazards may materialize at any time in a developing country.
- The responsibility for suicidal use of paraquat rests also on the manufacturer. Unrestricted access to a liquid of which a very small amount may be fatal makes a suicidal or parasuicidal decision easy.
- Regulatory agencies have not fully recognized either the inherent toxicity of paraquat for human beings or the particular risks derived from exposures in developing countries.
- Independent studies of occupational exposure assessment and health effects are needed.
- The impacts of interventions such as industry stewardship programs should be properly evaluated.
- Application of the precautionary principle to the regulation of pesticide use in developing countries would prevent many of the prevailing problems.
- The Central American Institute for Studies on Toxic Substances (IRET) will initiate an independent health risk assessment for paraquat in the Central American context.

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