

Paraquat and Marijuana: Epidemiologic Risk Assessment

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Abstract: In March 1978, 13 (21 per cent) of 61 marijuana samples from the southwestern United States were found to be contaminated with the herbicide paraquat, a pulmonary toxin, in concentrations from 3 to 2,264 parts per million. The source of the contamination was an aerial spraying program in Mexico, supported indirectly by United States funds. To evaluate US exposure, a nationwide survey of the paraquat content of confiscated marijuana was conducted. The survey found 33 (3.6 per cent) of 910 marijuana specimens to contain detectable paraquat. In states adjacent to Mexico (Census Region VI), 23 (12.8 per cent) of 180 specimens were contaminated. Combustion testing indicated that approximately 0.2 per cent of paraquat on marijuana passes into smoke. From

these data, we projected that 100-200 marijuana smokers in Census Region VI would be exposed by inhalation to 500 micrograms or more of paraquat per year, a dose judged to represent a health hazard; nationally, between 150 and 300 smokers were projected to have such exposure. Another 6,000 persons in Region VI and 9,000 nationally were projected to be at risk of exposure to between 100 and 499 micrograms of paraquat annually. The risk of paraquat exposure was greatest among those smokers who make one large purchase of marijuana per year. No clinical cases of paraquat poisoning were recognized among marijuana smokers during these studies, but no systematic national search for such cases was undertaken. (*Am J Public Health* 1983; 73:784-788.)

Introduction

A perennial problem in public health is the need to establish disease prevention policy on the basis of incomplete data. In issues as diverse as the setting of the occupational lead standard,¹ the adoption of guidelines for work with recombinant DNA,² and the distribution of potassium iodide to persons living near nuclear reactors,³ policy decisions were required well before all desired data were available.

Epidemiologic risk assessment offers a quantitative approach to the development of public health policy.⁴⁻⁶ In this technique, the number of persons who may be affected by a policy (or the lack of one) is calculated through the use of carefully defined decision rules and explicitly stated assumptions. The effects of policy options can be estimated by altering the decision rules or assumptions. As new data become available, the model may be modified.

In 1978, following the discovery that marijuana entering the United States from Mexico was contaminated with the herbicide paraquat, Congress directed the Secretary of the Department of Health, Education, and Welfare (HEW) to determine whether or not residual paraquat on marijuana represented a hazard to the health of marijuana users. This report describes the ensuing epidemiologic risk assessment undertaken by the Centers for Disease Control (CDC) and the National Institute of Environmental Health Sciences (NIEHS).

Toxicity of Paraquat

Paraquat (1,1'-dimethyl-4,4'-dipyridilium dichloride) is a widely used, rapidly acting herbicide.⁷ It appears to react within plant cells in concert with sunlight to generate superoxide radicals (O_2^-) which in turn destroy plant cellular membranes⁸ and desiccate the leaves. If sprayed plants are

harvested before exposure to sunlight, desiccation does not occur, and unaltered paraquat remains on the plant.

Paraquat is highly toxic to man. The lung is the principal target organ. Accidental or suicidal ingestion of only a very small dose (less than one teaspoon) of concentrated paraquat may produce irreversible progressive lung fibrosis.^{9,10} The case fatality ratio from pulmonary fibrosis following ingestion of concentrated solutions has been estimated to approach 50 per cent.¹¹ Other lesions produced by paraquat include irritative dermatitis, nail damage, eye injury, and severe epistaxis.¹²⁻¹⁵

The pulmonary toxicity of paraquat is enhanced when paraquat is inhaled or is administered directly into the lungs. Thus in experimental instillation studies, paraquat doses as low as 0.5 mg/kg in rats¹⁶ and one picogram (10^{-12} gram) in rabbits¹⁷ have been shown to produce localized areas of pulmonary edema and epithelial proliferation which progressed to fibrosis.¹³ The toxicity of inhaled paraquat appears to be a function of dose, duration of exposure, and particle size.¹⁸

Paraquat Spray Program

In 1975, the Government of Mexico began an aerial spraying program to destroy marijuana fields with paraquat, particularly in the Sierra Madre. From 1975 to 1978, the United States contributed approximately \$30 million per year to this program and to a companion program for eradication of poppies through spraying of 2,4-dichlorophenoxyacetic acid (2,4-D).^{*} United States monies were used solely for indirect support, such as for purchase and maintenance of aircraft; herbicides were purchased directly by the Government of Mexico.¹⁹

Mexican farmers apparently observed that the action of paraquat depended on sunlight. Accordingly, they began to harvest marijuana rapidly after spraying and to wrap the leaves in dark cloths for export to the United States.²⁰ No accurate estimates are available as to the quantity of paraquat-contaminated marijuana harvested.¹⁹

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* The poppy eradication program was highly successful and was associated with a sharp decline in importation of heroin into the United States from Mexico and with reduction in the number of reported deaths in the US due to heroin overdose from 1,770 in 1976 to 540 in 1977.¹⁹

TABLE 1—Amount of Marijuana Smoked per Week, CDC Telephone Survey, 1978

Grams* Smoked per week	Approximate Grams Smoked per Day	Number (Per Cent)
≤3	0.3	94 (18)
4–10	1	269 (51)
11–17	2	70 (13)
18–24	3	48 (9)
25–31	4	31 (6)
32–38	5	10 (2)
39–45	6	5 (1)
46–52	7	0
53–59	8	1
60–66	9	0
67–73	10	1
74–80	11	530 (100)

*One marijuana cigarette is assumed to contain one gram of marijuana.

Materials and Methodology

Initial Health Surveys

In March 1978, analyses conducted at the University of Mississippi showed that 13 (21 per cent) of 61 marijuana samples confiscated in California, Arizona, and Texas from October 1976 through August 1977 contained paraquat in concentrations from 3.3 to 2,264 parts per million (ppm).²¹ Also, preliminary data from the National Institute of Drug Abuse (NIDA) indicated that intact paraquat was detectable in the smoke from a one-gram sample of marijuana which had been treated with paraquat to a concentration of 450 ppm.²²

To evaluate the possible significance of those findings to public health, the CDC undertook localized surveys to determine if acute or chronic illness had been caused by paraquat-contaminated marijuana.²³ In an initial case-finding effort, CDC arranged for three West Coast clinics to interview marijuana smokers who presented with cough or other pulmonary symptoms and to obtain a sample of their marijuana for paraquat analysis. Thirteen persons with suspected toxicity were interviewed, and 12 samples were submitted; however, none of the samples was found to contain paraquat.

Additionally, CDC investigators conducted a telephone survey of 548 persons who had anonymously submitted marijuana samples to a California laboratory for paraquat testing.²³ This survey was intended to gather data on symptoms of possible paraquat toxicity and to correlate symptom prevalence rates with paraquat exposure; it was designed also to obtain information on patterns of marijuana purchase and use. The anonymity of participants was preserved. When the data were analyzed, symptom prevalence could not be correlated with paraquat exposure, because only one of the samples was found to contain paraquat. Data on marijuana consumption patterns (Table 1) were obtained, however. From those data, it was calculated that 17 per cent of the marijuana smokers who participated in this survey made only one purchase per year, whereas 35 per cent made nine or more purchases annually (Table 2).

The Percy Amendment

In August 1978, Senator Charles Percy (R-Ill.) introduced an amendment to Section 481 of the Foreign Assistance Act of 1961, prohibiting US support for programs involving spraying of herbicide to eradicate marijuana, if the use of herbicide "is likely to cause serious harm to the health

TABLE 2—Purchases of Marijuana per Year, CDC Telephone Survey, 1978

Purchases per Year	Number of Persons	Per Cent of Total
≤1.25	90	17
1.26–2.25	59	11
2.26–4.50	92	18
4.51–9.00	97	19
>9.00	184	35
TOTAL	522	100

of persons who may use or consume the sprayed marijuana."

Under the Percy Amendment, the Secretary of State was required to inform the Secretary of Health, Education, and Welfare of the use or intended use of any herbicide in a US-funded program. The Secretary of HEW was then required to determine potential health hazards. On October 13, 1978 the Department of State notified HEW that the United States was providing assistance to the Mexican program.

In response to that notification, then HEW Secretary Joseph Califano directed CDC to conduct a systematic sampling program to determine the extent and severity of paraquat contamination of marijuana. At the same time, he directed NIEHS to undertake additional combustion testing of paraquat-contaminated marijuana.²⁴ HEW legal staff reviewed the legislative history of the Percy Amendment to define the phrase "serious harm". They determined that no documentation of persons who had been damaged by exposure to paraquat was required, and that "actual harm need not be shown if it is reasonable to predict that it will occur."²⁵

Prevalence Survey

In November 1978, CDC initiated a nationwide program to obtain data on the prevalence of paraquat contamination of marijuana. Samples of confiscated marijuana were provided through the seven regional laboratories of the Drug Enforcement Administration (DEA) and by 14 local and state law enforcement agencies. Samples were received from 910 seizures covering the period 1975 through January 1979; of the 832 seizures for which the date of seizure was provided, 524 (63 per cent) were confiscated in the last quarter of 1978. DEA seizures accounted for only 15 per cent of all confiscations, but they were generally larger than the local interceptions and constituted 95 per cent of the total weight.

One-gram samples of each lot were analyzed by a reversed-phase, paired-ion high performance liquid chromatographic method developed at CDC with a detection limit of 5 ppm.²⁶ In interpreting the data, it was presumed that all of the marijuana confiscated in a seizure was from the same original source, and that the sample received was representative of the entire seizure.

Nationally, 33 (3.6 per cent) of 910 seizures or 1,059 (0.63 per cent) of 168,424 kilograms were found to contain detectable paraquat.²⁷ Seventy per cent of the contaminated seizures and 98.6 per cent of the total weight of contaminated marijuana was obtained in Census Region VI (New Mexico, Texas, Oklahoma, Arizona, and Louisiana). No contamination was found in specimens from the Eastern Seaboard or the Pacific Northwest. Paraquat concentrations in the 33 contaminated seizures ranged from 10 to 461 ppm (mean 111 ppm, median 52 ppm). Twenty-three (69.7 per

TABLE 3—Estimated Annual Paraquat Exposures for "Regular" Marijuana Smokers,* United States and Region VI, by Frequency of Marijuana Purchase, 1975–1979

Annual Paraquat Exposure (Micrograms)	Estimated Percentage (and Number) of Smokers with Exposure		
	United States—12 buys/year	Region VI—12 buys/year	Region VI—1 buy/year**
0	68.54 (6.85M)	29.5 (295,000)	87.17 (148,000)
1–99	31.32 (3.13M)	69.5 (695,000)	9.15 (15,600)
100–199	0.14 (14,000)	1.0 (10,000)	2.16 (3,700)
200–299	0***	0***	0.80 (1,360)
300–399	0***	0***	0.40 (680)
400–499	0***	0***	0.20 (340)
500–599	0	0***	0.10 (170)
600–699	0	0	0.02 (34)
700–799	0	0	0***
800–899	0	0	0***
900–999	0	0	0***
100+	0	0	0***

*It is assumed here that there are 10 million "regular" marijuana smokers in the United States, and 1 million in Region VI. It is further assumed that 0.2 per cent of paraquat on marijuana leaf passes unchanged into smoke.

**It is assumed that 17 per cent of marijuana smokers in Region VI make one purchase/year (Table 2).

***Approaching zero.

cent) of the 33 contaminated samples contained less than 100 ppm of paraquat, and only 2 (6.1 per cent) contained more than 400 ppm. The origin of 95 of the seized lots was known; 88 (92.6 per cent) had originated in Mexico.

Combustion Testing

The percentage of sprayed paraquat which passes unchanged into marijuana smoke was estimated by NIDA in July 1978 to be 0.2 per cent.²² Further combustion testing data produced under contract to the NIEHS also indicated that the 0.2 per cent figure was reasonably accurate.²⁸ Most of the paraquat was found to be pyrolyzed to 4,4'-dipyridyl.

Exposure Assessments

To estimate the potential exposure of smokers to paraquat in marijuana smoke, CDC undertook a series of computer-based epidemiologic risk assessments. These projections were based on the prevalence survey data, the combustion test results, and the telephone survey data on marijuana consumption patterns (Tables 1 and 2).

We recognized in making these projections that several factors could influence exposure to paraquat:

- Amount of marijuana smoked
- Amount of smoke inhaled
- Amount of paraquat in the smoke
- Amount of inhaled paraquat retained in the lungs
- The frequency of marijuana purchases
- The prevalence of paraquat-contaminated marijuana
- The concentration of paraquat in contaminated marijuana
- The geographic distribution of contaminated specimens

To obtain a national risk estimate of exposure to paraquat, we made the following, obviously somewhat arbitrary assumptions:**

- 1) That patterns of marijuana usage reported by persons who participated in the telephone survey were representative of those for marijuana users in general and that one marijuana cigarette contains one gram of marijuana;

- 2) That all of the smoke from a marijuana cigarette is inhaled;
- 3) That approximately 0.2 per cent of the paraquat on marijuana leaf passes unchanged into the smoke;
- 4) That all inhaled paraquat is retained in the lungs;
- 5) That regular marijuana smokers purchase 12 batches of marijuana per year;
- 6) That the national prevalence of paraquat-contaminated marijuana was 3.6 per cent;
- 7) That the distribution of paraquat concentrations in all contaminated marijuana was identical to that found in the 33 contaminated specimens examined by CDC; and
- 8) That contaminated batches of marijuana were uniformly distributed throughout the United States.

The number of micrograms of paraquat inhaled by one person during 1 year, assuming that one batch of marijuana is purchased and used during each month, was then calculated by the following equation:

$$\text{Inhaled paraquat} = .002 (n) (C_1 + C_2 + C_3 \dots C_{12}),$$

where .002 is the fraction of paraquat that passes unchanged into the smoke (0.2 per cent);
 n is the average number of grams of marijuana smoked per month;
 and C₁ through C₁₂ are the concentrations of paraquat on 12 separately obtained batches of marijuana purchased in the course of a year.

To replicate the probable distribution of lots which might confront the population of marijuana users who make 12 purchases per year, we generated randomly by computer 40,000 combinations of 12 batches each. These combinations were selected from a pool of 910 hypothetical marijuana batches, representing all of the batches received at CDC; 877 of these batches were considered untainted, and 33 (3.6 per cent) were considered contaminated with paraquat at the same concentrations as the specimens analyzed. All specimens in the pool were considered to have an equal likelihood of being selected; no allowance was made for variation in weight.

This model predicted that during one year 68.5 per cent of marijuana smokers in the United States would be exposed to no paraquat, that 31.3 per cent would inhale less than 100

** Alteration of any of these assumptions, such as those pertaining to cigarette weight, inhalation percentage, or smoke retention percentage would alter the risk assessment in linear fashion.

micrograms, and that approximately 0.1 per cent would inhale 100 micrograms or more (Table 3).

To evaluate possible paraquat exposure in Census Region VI, we undertook a second risk assessment. To reflect the regional nature of this survey, we modified assumptions 6 and 7 above, as follows:

- 6) The prevalence of paraquat-contaminated marijuana was considered to be 12.8 per cent; and
- 7) The distribution of paraquat concentrations was considered identical to that found in the specimens from Region VI.

In this assessment, 100,000 random combinations of 12 batches each were generated, and each combination was drawn randomly from a pool of 180 hypothetical batches (the number seized in Region VI), of which 23 were considered contaminated.

Not surprisingly, this model predicted that the pattern of exposure in Region VI would be quite different from that encountered nationally. Only 29.5 per cent of marijuana smokers in Region VI would be exposed to no paraquat in a year, 69.5 per cent (695,000) would inhale 1-100 micrograms, and approximately 1.0 per cent (10,000) would inhale 100 micrograms or more (Table 3).

We undertook further to assess the exposure risk of two subgroups of marijuana smokers in Region VI: 1) those who make only one large purchase per year; and 2) those who make 52 small purchases. In these assessments, we modified assumption 5 of the previous model such that the number of batches purchased per year was either 1 or 52, rather than 12. Each simulation was then based on 100,000 randomly selected combinations.

In contrast to the preceding assessments, we found among those marijuana users who make only one large purchase per year that there exists a small subgroup who have the potential to be quite heavily exposed to paraquat (Table 3). The actual size of this group is unknown, because only limited data are available as to the proportion of marijuana smokers who make a single purchase per year. Data from the CDC telephone survey suggest, however, that as many as 17 per cent of marijuana smokers may purchase their marijuana in this fashion (Table 2). Assuming that there are 1 million regular marijuana smokers in Region VI, and that purchasing patterns there are similar to those of the survey participants, then there may be approximately 170,000 once-a-year buyers in Region VI, of whom 100 to 200 would fall into the group whose estimated annual exposure to paraquat is 500 micrograms or more (Table 3). In addition, there would be approximately 6,000 persons among this group in Region VI who would be exposed each year to between 100 and 499 micrograms of paraquat. Similar calculations for the nation project that 150-300 marijuana users might inhale 500 or more micrograms of paraquat per year and that approximately 9,000 might inhale between 100 and 499 micrograms of paraquat annually.

The projections pertaining to buyers who make 52 purchases per year differ little from the results on those who make 12 purchases per year, except that there was a slightly lower prevalence in this group of zero exposures, a finding consistent with their 4.3-fold greater number of separate purchases.

Toxic Dose Estimate

To relate the above exposure estimates to possible health outcomes, we attempted to estimate a minimal toxic dose for chronic human exposure to inhaled paraquat.

Accurate human data on the quantitative toxicity of chronically inhaled paraquat do not exist. Previous studies of agricultural workers using paraquat have not examined the airborne concentrations to which the workers may have been exposed.^{12,29} Further, although one of those studies¹² performed serial chest x-rays on exposed workers and found no abnormalities over a 12-week period, it is important to note that the workers studied were using low-pressure spray equipment ("back-pack" sprays) which would have produced airborne droplets too large to have reached the workers' pulmonary alveoli^{12,18}; almost all inhaled paraquat would have precipitated in the workers' upper airways.

In the absence of relevant human data, we were required to extrapolate an estimate of minimal toxic dose from the available animal data. We were guided in that effort by the observation that man appears to be more sensitive to the effects of paraquat than are most animal species.⁹ Further, we knew that as little as one picogram of paraquat instilled directly into the lungs of rabbits had been shown capable of producing discrete pulmonary fibrosis.¹⁷

Finally, we recognized that our estimates of single-year inhalation exposure would tend to underestimate lifetime paraquat exposure, because many users smoke marijuana for more than one year. Based on these factors, we judged arbitrarily that an annual dose of 500 micrograms of inhaled paraquat was capable of producing pulmonary damage in exposed persons. We considered an annual dose of 100 to 499 microgram to convey a less serious, but still heightened risk of pulmonary injury. We did not consider the possible additional pulmonary injury which might result from the inhalation of 4,4'-dipyridyl, the principal combustion product of paraquat and a compound which has recently been shown to be itself a pulmonary toxin.³⁰

The Califano Decision

On April 2, 1979, HEW Secretary Califano concluded "that the spraying of marijuana with paraquat is likely to cause serious harm to the health of persons who may consume the sprayed marijuana."³¹ That decision was conveyed to the Department of State, and United States support for the Mexican program ceased.

Discussion

The major finding of the risk assessments described in this report is that each year from 1975 to 1979 100 to 200 marijuana smokers in the southwestern United States and 150 to 300 nationally were projected to have been exposed by inhalation to 500 micrograms or more of unaltered paraquat in marijuana smoke.

We found additionally that persons who make a single yearly purchase of marijuana are at greatest risk of paraquat exposure. This observation may have implications even for persons who make more frequent purchases, for if lines of supply are relatively stable, then users who make several purchases per year may obtain all of their marijuana from the same seller and same ultimate source.

During the present studies, we detected no acute or chronic cases of paraquat poisoning among marijuana smokers. This failure cannot, however, be taken as reassurance that exposure to paraquat-contaminated marijuana did not or might not in the future cause damage to the lungs of certain persons. There are several possible explanations for our failure to detect clinical cases. First, no active nationwide surveillance for such illness and no systematic screening of lung function in marijuana smokers was undertaken. Persons

made ill by exposure to an illicit drug are not likely to come voluntarily to the attention of public health authorities or to admit drug exposure even if they seek medical attention. Secondly, chronic pulmonary fibrosis is the most likely adverse effect of exposure to paraquat,³² and neither the time interval from onset of exposure to appearance of fibrosis, nor the cumulative dose which must be inhaled to produce pulmonary symptoms is known; the time from the beginning of the Mexican spray program to the time of this study may have been insufficient for chronic disease to have appeared. Finally, it appears that in the late 1970s many marijuana smokers in the United States may have changed from Mexican to domestic marijuana because of fear of paraquat exposure³³; thus population exposure to paraquat may have been reduced.

Marijuana smoke has itself been shown to be a pulmonary toxin. A recent report by a Committee of the National Academy of Sciences concluded that "chronic heavy smoking of marijuana causes inflammation and pre-neoplastic changes in the airways, similar to those produced by smoking of tobacco. . . . This suggests the strong possibility that prolonged heavy smoking of marijuana, like tobacco, will lead to cancer of the respiratory tract and to serious impairment of lung function."³² (The NAS Committee also concurred in our assessment of the potential health hazard to smokers of residual paraquat on marijuana.³²) The CDC, the NIEHS, and the other agencies of the US Public Health Service are seriously concerned about the hazards of marijuana and subscribe to the position that marijuana smoking is a hazard to health and ought to be discouraged. It should be noted, however, in the context of the present study, that HEW was not asked by the Congress to weigh the hazards of marijuana smoke against those of paraquat or otherwise to consider the benefits which might result from a herbicide spray program. Under the Percy Amendment, HEW was directed by the Congress solely to evaluate the possible health hazards of exposure to paraquat.

Epilog

On December 15, 1981, Congress repealed the Percy Amendment and appropriated \$37.7 million each year for fiscal years 1982 and 1983 for the renewed use of herbicides in international narcotics control. These funds may be expended in various nations and apparently will not be limited to Mexico.

The US Department of Health and Human Services (successor to HEW) has been given responsibility for monitoring the impact on health of the renewed spraying program. The techniques of epidemiologic risk assessment described in this report can be applied to that monitoring. However, the model may need to be altered by forthcoming survey data to reflect: 1) possible increases in the prevalence of paraquat contamination which may result from multinational spraying; and 2) possible resultant changes in the regional distribution of paraquat-contaminated marijuana within the United States.

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