

# Cutaneous Toxicity and Absorption of Paraquat in Porcine Skin<sup>1</sup>

VAGDEVI SRIKRISHNA, J. EDMOND RIVIERE, AND NANCY A. MONTEIRO-RIVIERE<sup>2</sup>

*Cutaneous Pharmacology and Toxicology Center, North Carolina State University, 4700 Hillsborough Street, Raleigh, North Carolina 27606*

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Paraquat, a commonly used herbicide, has been shown to be toxic in exposed field workers. The objectives of this study were to (a) assess the cutaneous toxicity of paraquat *in vivo* in pig skin and *in vitro* in the isolated perfused porcine skin flap (IPPSF) and (b) quantitate its absorption in the IPPSF. The amounts of 3, 24, and 200 mg of paraquat were topically applied (5 cm<sup>2</sup> surface area) on the ventral abdomen of pigs and biopsied after 6-8 hr for light microscopy (LM) and transmission electron microscopy (TEM). IPPSFs were topically dosed with the same concentrations and perfused for 8 hr (*n* = 4/treatment). The dosed area of the skin was sampled for LM, TEM, and enzyme histochemistry. IPPSFs were also treated topically with [<sup>14</sup>C]paraquat dichloride at the aforementioned concentrations (*n* = 4/dose) and hourly perfusate samples were collected for radiolabel determination and assessment of biochemical and physiological parameters. The epidermal changes were similar both *in vivo* and *in vitro*. The changes included epidermal intercellular edema which increased with dose and epidermal-dermal separation at the 200-mg dose. Acid phosphatase and nonspecific esterase activities were increased in the upper layers of the epidermis, while alkaline phosphatase showed a greater activity in the stratum basale layer. Glucose utilization of all treated IPPSFs was lower than that of the controls and a variation in the vascular resistance profiles was seen in all the treated flaps. Radiotracer studies indicated that a majority of the compound remained on top of the application site and minimal absorption or penetration into skin was observed. Thus, at high concentrations and prolonged exposure, paraquat may have deleterious effects on epidermal morphology in the absence of significant percutaneous absorption. © 1992 Academic Press, Inc.

Paraquat (1,1'-dimethyl-4,4'-bipyridinium dichloride) is a contact herbicide which is widely used in the agricultural industry to aid in the harvesting of a wide variety of crops. Approximately 5 × 10<sup>6</sup> hectares are sprayed annually with paraquat in Europe alone (Sagar, 1987). Its widespread use

stems from its usefulness as an effective nonselective weed eliminator (kills a wide variety of monocots and dicots). Paraquat was first introduced in Great Britain in 1962 and became commercially available in the United States in 1964. It is a hydrophilic compound available in granular and liquid forms (Kimbrough, 1974). Paraquat is a permanently charged cation and is dissociated at all pH values (Clark *et al.*, 1966). Its contact herbicidal properties have advantages over other foliage-applied translocated herbicides. The major environmental concern of pesticide/herbicide residue is not of significance in the use of paraquat since it is easily inactivated upon contact with soil or sunlight. Despite its usefulness, paraquat is a well-known lung, nail, and ocular toxicant (Cant and Lewis, 1968; Samman and Johnston, 1969). The major cause of systemic toxicity leading to death is accidental oral ingestion.

The systemic effects and the mechanisms of action have been well studied (Clejan and Cederbaum, 1989; Rosen *et al.*, 1989). Paraquat is a potent free radical generator (Juchau *et al.*, 1986) and is actively accumulated by various tissues such as lung and brain. It competes with natural oligoamines in the body for its uptake and accumulation (Nemery *et al.*, 1987; Wyatt *et al.*, 1988).

There have been relatively few cases of fatality due to dermal exposure of paraquat (Smith, 1988; Athanaselis *et al.*, 1983; Tungsanga *et al.*, 1983). Even though various dermal absorption studies have been conducted (Chui *et al.*, 1988; Dey *et al.*, 1990; Scott *et al.*, 1986; Tabak *et al.*, 1990), and clinical cases of dermal necrosis have been reported, there is a dearth of information regarding detailed morphological changes seen upon topical exposure through skin.

It is well documented that porcine skin closely resembles human skin both structurally and functionally, and the isolated perfused porcine skin flap (IPPSF) has been proven to be a useful alternative *in vitro* model for the study of direct cutaneous toxicity (King and Monteiro-Riviere, 1990; Riviere *et al.*, 1986; Monteiro-Riviere *et al.*, 1987; Monteiro-Riviere, 1990b). Topical absorption, penetration, and quantification of various chemicals and drugs have been extensively studied and the results have shown an excellent correlation to human studies and other *in vivo* situations (Carver *et al.*, 1989; Williams *et al.*, 1990; Riviere and Monteiro-Riviere, 1991). It is, therefore, the objective of this paper to describe the morphological changes seen upon top-

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<sup>2</sup> To whom correspondence should be addressed at NCSU-CVM Box 8401, Raleigh, North Carolina 27606.

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