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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

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MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: EPA No. 239-2186, Specialty Studies of the Oral Corrosion and Dermal Irritation Potentials of Paraquat CL
Tox. Chem. No. 634

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The Toxicology Branch has reviewed two specialty studies submitted by the Chevron Chemical Company:

1. The Comparative Oral Corrosion Potential of Aqueous Dilutions of Paraquat CL in Adult Male and Female Rabbits.

2. The Comparative Four-Hour Skin Irritation Potential of Aqueous Dilutions of Paraquat CL

The oral study demonstrated that Paraquat CL causes local corrosion of the tongue, and (to a lesser extent) the esophagus and stomach following dosing on the tongue. It was corrosive to the tongue at dilutions as small as 1:100. Other affected organs were the larynx, lungs, liver, and kidneys. Laryngeal lesions were observed at dilutions as small as 1:200.

The skin irritation study demonstrated that neat Paraquat CL is moderately corrosive (PIS = 3.9), and dilutions as small as 1:200 are slightly irritating (PIS = 0.3). The lesions were reversable only at the 1:200 dilution level.

Reviews of these studies are attached.

Comparative Oral Corrosion Potential of Aqueous Dilutions of Paraquat CL in Rabbits

Chevron Environmental Health Center; Report No. SOCAL 2034; August 31, 1983

PROTOCOL: Groups of 4 male and 4 female New Zealand White rabbits (males - 1.6-2.48 kg; females 1.79-2.58 kg) were fasted for 24 hours, then orally dosed with Paraquat CL (28.6% a.i.; 20.7% cation; Lot No. SX-1420). Serial aqueous v/v dilutions were administered at the following concentrations:

Vehicle control (water)	
Neat (undiluted)	1:25
1:2	1:50
1:5	1:100
1:10	1:200

One ml aliquots of the test formulations were placed on the base of the tongue. Each rabbit was examined twice daily for clinical signs. Half of the males and half of the females were sacrificed 24 hours after dosing and the remaining rabbits were sacrificed 96 hours after dosing. Each rabbit was examined grossly. The esophagus, stomach, tongue, and pharynx were examined for erythema, edema, necrosis, or other lesions. These lesions were not assessed for severity. The esophagus, stomach, tongue, and pharynx and any other abnormal tissues (liver, lung, and kidney) were fixed and examined microscopically by Veterinary Pathology Consultants, Inc. Oral corrosion potential was evaluated by the following criteria (quoted):

Negative - No gross erythema, edema, necrosis and/or microscopic injury when examined at 24 and 96 hours.

Irritant - Patchy area of erythema with or without edema present at 24 hours but not at 96 hours. Microscopic examination of tissue from the animals sacrificed at 96 hours should be normal in appearance.

Corrosive - Necrotic lesions at 24 or 96 hours confirmed by microscopic examination. Since the test is primarily concerned with corrosive action, it shall be considered corrosive if any of the test animals at 24 or 96 hours show signs of necrotic lesions in the mouth, pharynx, larynx, or esophagus. The extent of injury is confirmed by histologic examination.

RESULTS: Rabbits dosed with neat test article or the 1:2 dilution died between day 1 (approximately 18 hours) and day 3. A female given the 1:5 dilution died on day 3. Clinical signs included anorexia, decreased motor activity, weakness, rales, and dyspnea, which were observed in both sexes at concentrations of 1:25 or stronger.

No gross lesions of the mouth, pharynx, larynx, or esophagus were seen in the vehicle controls nor in the rabbits given dilutions of 1:25 - 1:200. The rabbits given dilutions of $\geq$1:10 had no tongue or stomach lesions at the 24 hour sacrifice, but frank erythema and/or edema were seen in the pharynx and esophagus of rabbits given the neat formulation and in the esophagus of 2 males and 1 female in the 1:10 dilution group. "Equivocal changes" were seen

in the esophagus of the 1:2 dilution group, and in the pharynx of one female in the 1:10 dilution group. In those rabbits in the neat and 1:2 dilution group which died on days 2-3, erythema and/or edema involved the tongue (neat and 1:2 dilution), pharynx (neat and 1:2 dilution), esophagus (neat and 1:2 dilution), and stomach (neat). In addition some equivocal changes were seen in the pharynx, esophagus, and stomach of some rabbits in these 2 groups. The tissues of 2 rabbits which died on day 2 were too autolyzed for evaluation. The surviving rabbits examined at 96 hours (i.e. the 1:5 - 1:200 dilution groups) had no gross lesions of the tongue, pharynx, esophagus, and stomach.

Other gross observations at the 24 hour sacrifice included grainy, blanched, or mottled livers in the neat and 1:2 dilution group and Grey, mottled, hemorrhagic, or "liver-like" lungs at dilutions as low as 1:100. Animals sacrificed at (or dead before) 96 hours had liver and red or grainy kidney lesions in the neat, 1:2, and 1:5 dilution groups, and lung lesions at dilutions as low as 1:100. A greater percentage of rabbits had lung involvement at the latter sacrifice interval. Microscopic lesions generally corresponded to the gross findings and were dose-related. They included the following:

Tongue - Ulcerative/necrotizing glossitis; Epithelial mucosal degeneration/necrosis

Pharynx - Acute/ulcerative pharyngitis

Esophagus - Epithelial mucosal degeneration/necrosis; Ulcerative esophagitis

Liver - Chronic cholangitis; necrotizing hepatitis

Kidney - Tubular degeneration/necrosis

Lung - Necrotizing pneumonia; Congestion/edema; Pulmonary hemorrhage

The tongue and pharynx were the most affected tissues with lesions occurring as low as the 1:100 dilution for tongue, and the 1:200 dilution for pharynx. Very few rabbits had esophageal or kidney lesions. The few sporadic stomach lesions were probably not compound-related. Other than chronic cholangitis in 4 of 6 rabbits in the neat group, hepatic involvement was minor. Although the lungs were not involved in the dosing exposure or excretion, pulmonary lesions were evident. The lungs are well documented as a systemic target organ for Paraquat. Five of 6 neat group rabbits had congestion/edema, and lesser numbers of rabbits had necrotizing pneumonia (at $\geq$1:10 dilutions) and pulmonary hemorrhage (at $\geq$1:5 dilutions). Although it was not clear in the histopathology tables, the text of the report defined the abovementioned pharyngeal lesions as actually being found in the laryngeal epithelium which was not directly exposed during the dosing procedure.

CONCLUSIONS: The dosing of Paraquat CL on the tongues of rabbits at dilutions as low as 1:100 caused localized corrosion. Corrosion and irritation in the esophagus and stomach were diminished in comparison, probably due to dilution by body fluids. The high incidence of pharyngeal (defined as laryngeal epithelium) lesions which were seen at dilutions as low as 1:200 were attributed to aspiration by the report. It is unlikely that sufficient material could be aspirated to cause laryngeal lesions as extensive as were seen in this study. Therefore, the laryngeal epithelium as well as the lungs are proposed as systemic target organs.

This study is ACCEPTABLE. The consulting pathologist failed to define the scoring method used, and the Quality Assurance inspectors identified only as "M.I." and "E.T." failed to sign the Quality Assurance Statement. The summary pathology table failed to differentiate between the two sacrifice intervals, thus making interpretation difficult. Lesions of the laryngeal epithelium were defined as "pharyngeal." This made it appear as though the lesions seen were caused by contact corrosion resulting from the oral dosing.

Comparative Four-Hour Skin Irritation Potential of Aqueous Dilutions of Paraquat CL in Rabbits

Chevron Environmental Health Center; Report No. SOCAL 2035; September 9, 1983

PROTOCOL: Eleven female New Zealand White rabbits (10-12 weeks old) were dermally dosed with Paraquat CL (28.6% a.i.; 20.7% cation; Lot No. SX-1420). They were dosed with 0.25 ml aqueous v/v dilutions on the shaved skin of their backs. The dilutions used were as follows:

Neat (undiluted)	1:25
1:2	1:50
1:5	1:100
1:10	1:200

Ten rabbits were dosed with each of three randomly selected formulations, and the eleventh rabbit was dosed with two randomly selected formulations. A total of 4 dosing sites were treated with each formulation. No vehicle control sites were used. The dosing sites were unoccluded and the rabbits wore collars to avoid tampering. After 4 hours of exposure, the dosing sites were rinsed with distilled water and wiped clean. The dosing sites were scored for irritation by the method of Draize at 1, 24, 48, and 72 hours and 7 days after dose removal. After the final scoring, the rabbits were sacrificed and each treated area of skin was evaluated histopathologically by Veterinary Pathology Consultants, Inc.

RESULTS: Dose-related erythema and edema were seen at all concentrations tested. At concentrations >1:25, the irritation slowly worsened during the study. The primary irritation scores were as follows:

Formulation -	Neat	1:2	1:5	1:10	1:25	1:50	1:100	1:200
PIS -	3.9	3.8	2.9	3.0	2.8	1.1	0.6	0.3

Erythema contributed most to the scores and ranged from slight to moderate. Edema ranged from no edema to well-defined with definite raising. Only the 1:200 dilution sites had all reversed by day 7.

Dose-related microscopic lesions included slight to moderate acanthosis (>1:100 dilutions), mild to moderate ulcerative dermatitis (>1:10 dilutions), slight to mild non-suppurative dermatitis (1:2 - 1:100 dilutions), and slight to mild hyperkeratosis (1:2 dilution only). In addition there were some cases of focal destruction of hair follicles in skin treated with the neat, 1:2, and 1:10 dilutions.

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This study is CORE MINIMUM - Toxicity Category III. The Quality Assurance inspector identified only as "M.I." failed to sign the Quality Assurance Statement. There were several rounding errors in the tables. EPA guidelines recommend using double the volume of test article per dose (i.e. 0.5 ml). Vehicle control test sites were not used.

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