PQ Trade

Richmond, CA
October 13, 1976

PARAQUAT EMETIC
File: 152.31 - Paraquat

MR. J. N. OSPENSON
Chevron Chemical Company

I have reviewed the information given to us by ICI on P.P. 796 (the paraquat emetic). This compound is referred to in the reports as ICI 63,197, and the structure has been verified by Hans Franke as that given to him at Jealott's Hill.

I am somewhat confused by my review. On page 1 of the draft attached to John Braunholtz's letter of 4 August 1976, the following statement is made: "The level of inclusion of P.P. 796 in Gramoxone has, after careful consideration of human data, been established as 0.05% w.v. This will give a dose of 5 mg in 10 ml of Gramoxone which is likely to produce emesis within 15 minutes in 80% of those ingesting such a quantity."

The only information we have regarding human experience with this drug is a report titled "A Summary of Clinical Results of the Phosphodiesterase Inhibitor ICI 63,197 in a Variety of Disease States" dated 23 July 1973 and authored by P.F.C. Bayliss.

It has been confirmed by Peter Slade (by telex) that this report is the sole documentation of emetic action in humans. This report summarizes 11 different experiments in normal and diseased human volunteers. A summary of the induction of emesis follows:

Study Number	Dose (mg)	Number Vomiting/Number Tested
1	0.25	0/1
	0.5	0/1
	1.0	0/2
	2.0	0/3
	3.0	0/2
	4.0	1/2 (30 minutes)
	8.0	1/1 (2 hours)
2	2.0	1/8 (45 minutes)
3	2.0	0/2
4	2.0	1/4 ? (patient described as "sick")
5	2.0	1/2 (20 minutes)
6	No information given on dose or side effects.	
7	2.0 TDS x 21 days	0/4
8	1.0 TDS x 7 days	
	+2.0 TDS x 7 days	0/6
9	1.0 TDS x 7 days	
	2.0 TDS x 7 days	1/5
10	2.0 QDS x 4 weeks	0/3
11	2.0 TDS x 6 weeks	0/4

As you can see, these data do not support the statement made in Braunholtz's letter and confirmed in Slade's telex. As far as I can tell, no one has vomited within 15 minutes.

The data used to support the efficacy of emetic in paraquat given to the dog and monkey show dose levels of 2 or 3 mg/kg of the emetic. The dose in mg/kg for the 2 mg dose in humans was 0.036 mg/kg, for 3 mg was 0.038-0.042, for 4 mg 0.05 and for 8 mg was 0.1 mg/kg. The 5 mg dose would be about 0.06 mg/kg for a 170-lb. man. This is significantly lower than the 2-3 mg/kg found effective in the dog and monkey. At CTL, I was told that the compound was more active in humans, but the data does not support this.

The second area which concerns me is the matter of the effects of ICI 63,197 itself, both in man and animals. In man, the drug was associated with angina pectoris (a symptom of cardiac injury), worsening of psychic depression in depressed persons and transient increased capillary fragility. The most commonly reported side effects were nausea, flushing and dizziness. In animals, ICI 63,197 caused a decrease in agility and motility, potentiated both amphetamine and barbitone (drugs whose actions are in opposite directions!), decreased sensitivity to pain and heat, and decreased appetite. Many of these effects were seen in mice at acute doses as low as 0.1 mg/kg.

This presents a picture of a very active compound, and one whose action is difficult to classify. There is no question that this compound has effects on the central nervous system in both man and animals. Studies on sub-acute toxicity did not address themselves to these effects and thus no measure of the sub-acute effect on the CNS is available.

I am skeptical that EPA would approve this drug for use as an inert given the above-stated lack of information on either efficacy in man (as an emetic) at suggested levels or of the chronic effects of low exposure on the circulatory and central nervous systems.

In my opinion, we need to give a 5 mg dose to a large number of humans to substantiate the effectiveness of this dose, and probably, to repeat 90-day studies at low doses and measure motility, agility, amphetamine toxicity and barbitone hypnosis time as well as the classic indicators of toxicity.

J. A. SPENCE

By Original Signed
R. D. CAVALLI
R. D. Cavalli

RDC:flm

cc: Mr. H. Franke
Mr. R. E. Rodman
Mr. L. R. Stelzer