

Dr D Seaman
P P L
J H R S

Mr A W Waitt)
Mr E G Schumacher) Fernhurst

Mr M G Ashley Yalding

Mr D Ganderton Pharmaceuticals

Dr D M Ferguson I H R L

KF/AMR

28 Nov 72

PARAQUAT - SAFER FORMULATIONS

The approach to the problem of safer formulations seems to me to fall under two headings:

- (1) To deter drinking
- (2) To reduce toxicity

The first of these can be dealt with urgently and includes the mixotrope, colouring smells etc. The second involves a considerably longer period and even if feasible would not be available for at least another year.

May I cover the specific points raised in your letter.

- (1) Emetics. There are two basic types (a) general irritants to the alimentary tract. These are usually fairly fast acting and include the metallic compounds, ie zinc and copper salts and potassium antimony tartrate (tartar emetic). The drawback to these is that the effective dose is around 1 g which would have to be present in 5-10 ml of Gramoxone; (b) centrally acting compounds such as apomorphine and Pharmaceuticals ICI 63,197. These are effective in low doses (c 10 mg) but are expensive. Also they depend on being absorbed into the general circulation and acting on the brain; they therefore tend to be slow in action, say 15-30 minutes. I have spoken to Dr Bayliss of Pharmaceuticals Division who agrees that emetics are unlikely to be of help and also tells me that ICI 63,197 has rather nasty side-effects although these may not be of much consequence in paraquat poisoning. I cannot say these compounds will be ineffective but I think that such additions will be very expensive and of marginal use. Dr Bayliss knows of no new compounds in this field.
- (2) Wetters. Our experiments indicate that the addition of cationic wetters to paraquat increases the toxicity to dogs by a factor of 5-10. It may also do the same in monkeys; it has no such effect in rats and guinea pigs. There is a slight indication from excretion data that man does not behave like the dog but this is by no means certain. If man is like a dog I would expect omission of the appropriate wetter to have a significant effect, even allowing that many people probably take several lethal doses. Whether it would be more or less significant than deterrent formulations is complete speculation.

FROM: K Fletcher

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TO: Dr D Seaman

28 Nov 72

- (3) It is possible that compounds exist which reduce uptake but we have no information and to try to discover these would be quite a considerable effort and certainly lengthy.
- (4) Bittering agents could be added cheaply. I do not think Gramoxone is bitter itself but I doubt if a taste is sufficiently deterrent since by the time it is tasted it is too late. It might, however, be reasonable to add Bitterex since it is very cheap and does no harm.
- (5) The hope of increasing renal flow is I think a non-starter. Such agents would be of short duration and expensive and I doubt whether they would be effective.

In general I do not think there is any great future in trying to reduce the toxicity of Gramoxone except by considerable dilution. We should therefore concentrate on reducing the hazard and the present ideas on formulation are all possible steps. We have a considerable amount of sympathy for our position and if we do something sensible, even though it proves not to be very effective, we would be seen to be trying. At the moment I would sympathise with a registration authority that said it was trying its best without very much support from ICI.

K Fletcher