

PARAQUAT/EMETIC : Points for presentation to FDA

1. Paraquat is one of the most widely used herbicides in global agricultural practice several thousand tons being used annually since its introduction in 1963.
2. Sale is restricted to bona fide agricultural users who purchase an aqueous concentrate containing between 20 and 30 per cent paraquat ion.
3. Prior to application the concentrate is diluted with water at least a hundred fold.
4. Pure paraquat has an LD₅₀ (rat) of ¹⁶⁰150 mg/kg.
5. When used as directed paraquat presents no hazard to the user. However there are instances of deliberate ingestion of concentrate with suicidal intent or occasions when death has resulted from the accidental ingestion of concentrate transferred to an unmarked container, e.g. a Coke bottle. Death usually results from pulmonary failure, the minimum lethal volume of concentrate being approximately 15 ml. Ingestion by suicides is believed to involve volumes of, on average, 50 ml concentrate.
6. As a consequence of its use as a suicide agent (approx. 100 deaths per annum) and accidental ingestion, ICI (UK) and Chevron (USA) have sought ways of altering the presentation of the concentrate. Clearance has recently been given by the EPA to add n-valeric acid as a stenching agent which will have the effect of forewarning persons potentially in a position to ingest the concentrate accidentally. The position regarding suicidal intake can only be affected by making it impossible to absorb paraquat.
7. The Pharmaceuticals Division of ICI (UK) in its search for compounds for the control of asthma identified ICI 63197 (also designated PP796) as a candidate. Toxicological data necessary for support of human clinical evaluation was obtained and being fully satisfactory to the Committee for the Safety of Medicines (UK), clearance for trials was granted.
8. PP796 was discovered, on the basis of the human studies, to be an emetic agent of considerable potency for which reason its development as an anti-asthmatic drug was terminated.
9. PP796 has now been examined as an additive to paraquat concentrates with a view to its producing emesis if such a concentrate is ingested. Data on the paraquat/PP796 combination in vomiting species (dog and cynomolgus monkey) have shown clear evidence for the life-saving potential of the mixture.
10. The following aspects of PP796 make it a compound of choice for the intended paraquat combination. No previously known emetic agent meets these criteria.
 - (a) It is stable in the presence of paraquat.
 - (b) It has a clean toxicological profile.
 - (c) It is more potent than any established emetic.
 - (d) At 100-fold emetic dose there are no side effects in monkeys, i.e. an LD₅₀ in a vomiting species cannot be obtained.

- (e) It is not absorbed through unbroken skin and represents no hazard to the operator.
- (f) It is rapidly metabolised in mammals with a human serum half-life of 3.5 hours.
11. It is important to note that humans will only ever ingest PP796 as a consequence of suicidal or accidental intake. PP796 will be present at a concentration of 0.05% the ratio to paraquat being 1:400. This concentration represents 7.5 mg in an average mouthful (15 ml.).
12. In cases of paraquat poisoning the toxic symptoms are not often seen for several hours after ingestion. The rapid action of PP796 should provide an indicator enabling medical treatment to be put in action earlier.
13. The new formulation is to be sold by ICI world-wide. Registrations are being progressed to this end, approval having already been granted in the UK and France through the normal pesticide regulatory procedures. A number of European Poisons Centres have welcomed this positive step at hazard reduction. The formulation is now on sale in the UK.

Summary

The addition of a powerful, safe emetic agent to paraquat formulations will, it is believed, be instrumental in saving the lives of individuals who either with suicidal intent or accidentally ingest paraquat. ICI and Chevron anticipate that this measure will curb the increasing use of paraquat as an agent of suicide. The only occasion of human ingestion of PP796 will be under these rare circumstances and, for this reason we do not believe that this compound should be regarded as a drug per se but in its conjunction with paraquat. The petition for registration should thus be regarded as an extension of an existing registration.

D M Foulkes
9.6.77

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ICI PLANT PROTECTION DIV. JEALOTTS HILL

Amendments to Paraquat / Emetic: FDA
Presentation

1) Page 2 Item 11
Last sentence add: "of product.
The product is diluted 100 fold before
field use - see item 3."

2) Summary
(i) Delete second sentence
"ICI + Chevron agent of suicide"
~~to~~
(ii) 3rd sentence, full stop after per se
and delete "but in its conjunction
with paraquat."

Thanks

Appreciate copy of final Calderbank
document by same route (infotec) rapifax if
possible

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