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| Your ref | Our ref | Tel ext | Date |
|---|---|---|---|
| | GCW/SAH | Redacted-EU PII | 18 NOV 1983 |

Dear Dr Jager

IPCS ENVIRONMENTAL HEALTH CRITERIA DOCUMENT : PARAQUAT

In August ICI received by various routes copies of the draft of the IPCS EHCD on paraquat and diquat. At that moment our resources were already heavily committed to other projects and we were not therefore in a position to comment by a mid-September deadline which we were given by some of our points of contact. However, we have now been able to give the document our attention and would like to offer the following remarks for consideration by your team which we anticipate will meet to review the draft during the week beginning 5 December.

The following comments relate to the text on paraquat. We are commenting separately on the diquat text.

Inevitably the weight of the comments which follow relates to points which we think should have been tackled differently. Therefore, it is appropriate that I should preface them by the overall remark that we are not especially critical of much of the main body of the draft, viz Sections 2-9, on which overall your drafters are to be complimented. The Summary (Section 1) gives the impression of having been written separately, perhaps by someone with a less intimate knowledge of paraquat than in the case of the main body of the document; that is unfortunate since many readers will be most influenced by the summary of any document. Therefore, we would urge that particular consideration be given to our comments on the summary (see below).

One other overall point which needs to be made is that particular attention needs to be paid to the referencing. There are instances wherein authors names are given incorrectly, years are shown wrongly or even where a reference cited does not appear in the references list. I will mention some of the cases we noticed during our detailed comments (see below). Meanwhile, the existing inaccuracies detract from the scientific standing of the document and we would, therefore, urge that somebody within your team be given the task of checking carefully and individually each of the references cited, both in the text and in the references list of the final document.

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Several of our comments relate to a referencing of ICI proprietary unpublished data which have not been submitted by ICI to IPCS for the purposes of this review. Since those documents are not available indiscriminately from ICI to any person who asks for them may we recommend that, in those instances wherein the reports had already been reviewed by the JMPR, the referencing be changed to cite the appropriate JMPR review? There remain a few such reports which are useful to the IPCS review but which have not been reviewed by the JMPR; in those instances we will not object to the ICI unpublished data being referenced. The changes in referencing which we propose are summarised in Appendix I to this letter.

The following are our detailed comments on the text. IMPORTANT - I have underlined the page and line numbers where we deem the comment to be major.

1. Summary and Recommendations

(See end of this letter).

2. Properties and Analytical Methods

Page 10, line 5. The major manufacturer is not making the di(methylsulphate) salt.

Page 10, line 17. Paraquat is NOT combustible. It does not cause fire and explosions and we question the validity of the implication that toxic gases and vapours may be released at above 180°C. The corresponding text on diquat on page 96, lines 11-13 more fairly represents the situation which also applies to paraquat.

Page 10, line 30 to page 12, line 1. We recommend :

nite in 0.1 N NaOH. The absorbance of the resulting blue cation measured at 600 nm can be used as a measure of the paraquat concentration. Diquat does not interfere because its radical cation is green in colour. For residue level determinations (eg sub ppm levels) the higher intensity absorption at 396 nm for the paraquat radical and the 379 nm for the diquat radical are more commonly used. Calderbank and Yuen.....

Page 11. Table 2. Under "water", Calderbank and Yuen (1965) should appear. The remark is also applicable to page 12, line 21. "Soil" appears twice in Table 2.

Page 12, line 3; page 13, lines 19-21. We recommend that sensitivity "down to" is better than "up to".

Pages 12 and 13. The use of units (ug/ml : ug/g : ppm) is not consistent.

3. Sources In The Environment

Page 14, line 14. 'GRAMOXONE' should be shown as a trade name. ICI is now "plc" rather than "Ltd".

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Page 14, line 22 to page 15, line 2. We recommend that only compounds specifically listed in the FAO Specification be mentioned, at either maximum permitted levels or at "less than" levels (rather than "not present"). The final sentence of the paragraph relates to the proprietary ICI reference (ICI, 1978) which has not been submitted to IPCS for review by ICI. We recommend that the sentence and reference be deleted.

Page 15, lines 13-16. Various views, sometimes conflicting, were presented at the 1978 CCPR on the relative safety of the dichloride versus di(methylsulphate) salts, as indicated to some extent by paragraphs 118-120 of ALINORM 79/24. Since ICI is not selling the di(methylsulphate) salt we have no vested interest but we wonder about the strength of the defence which IPCS would be able to muster in the event that the document is later criticised on the grounds that the text does not constitute a balanced reflection. Since little, if any, di(methylsulphate) is being sold anyway, it might be less controversial to omit the two sentences.

Page 15, line 20. GRAMOXONE does not contain corrosion inhibitors.

Page 15, lines 24-25. "... are more resistant. GRAMOXONE S, a formulation without surface active agents, is used as an aquatic herbicide." The reference to GRAMOXONE S being produced for aerial application is wrong. ICI no longer produces the special formulation, AERIAL GRAMOXONE.

Page 15, lines 38-39. The final sentence of the foregoing comment refers.

Page 16. PARACOL should be shown as 10% (not 20%). PATHCLEAR now contains 3-aminotriazole as well as simazine. PREEGLONE containing 12% paraquat is sold in France and Belgium in addition to Spain. WEEDOL is sold in the Netherlands. The correct terminology for 'Holland' is 'The Netherlands' and for 'Eire' is 'Ireland'.

4. Environmental Distribution And Transformation

Page 18, lines 8 and 11. For "(Clark 1965)" and "(Broadhurst et al 1966)" read "FAO/WHO, 1971" - see Appendix 1.

Page 18, line 17. For "(Baldwin and Griggs, 1971) "read "(Calderbank and Slade, 1976)" - see Appendix I.

Page 18, lines 18-20. We question the validity of the claim that UV degradation of herbicide reaching the soil should be regarded as insignificant (see next comment). Therefore, we recommend that the paragraph be terminated in line 18, at the word "period".

Page 19, lines 20-22. We question the validity of the claim that microbial degradation is of minor environmental significance. There is increasing evidence that strongly-bound paraquat residues are degraded in soil with time, albeit at rates of 5-10% per annum (eg Hance 1980 see below). The mechanism of degradation is not yet understood and thus the contribution of photochemical degradation and of microbial degradation is uncertain. However, they should not be belittled at present since even a degradation of 4-10% per annum is significant in the longer term. We recommend re-wording the sentence :

/....

"Microbial degradation of paraquat in the field is therefore relatively slow."

Page 19, lines 25-26. The opening sentence would read better :

"Paraquat is rapidly and strongly bound to soil clay minerals."

Page 20, line 11 : "... 20 ppm in equilibrium solution), the ..."

Page 20, line 13 to page 21, line 6. We had major criticisms of the draft text and, for brevity of explaining our views, would offer for consideration the following text to replace the existing two paragraphs :

As summarised in Section 4.2, free paraquat is degraded by a range of micro-organisms. However, degradation of strongly adsorbed paraquat is relatively slow. In pot studies degradation is very slow or non-detectable (Riley et al 1976). However, in longterm field studies degradation rates were 5-10% per year. This is greater than the rate required to prevent saturation of the deactivation capacity of soils.

In a longterm trial on a loamy soil, plots were treated with 0, 90, 198 and 720 kg paraquat/ha, which was incorporated to a depth of 15 cm. These rates were equivalent to 0, 50, 110, 400% of the soils strong absorption capacity (Gowman et al 1980, Wilkinson 1980, Riley 1981). Over the 7 years paraquat residues declined by 5% per year (sig P = 0.05) on the 90 kg/ha plots and by 7% per year (sig P = 0.01) on the 198 and 720 kg/ha plots. The rate of decline on the 198 and 720 kg/ha plots was significantly greater (P = .01) than on the 90 kg/ha plots.

In another longterm trial on a sandy loam plots were treated annually with 4.4 kg/ha for 12 years (Hance 1980). The rate of loss of paraquat soil residues was about 10% per year and the soil residues tended towards a plateau level where the rate of application equalled the rate of degradation. Data for the last 4 years (total 16 years) has confirmed the early results (Hance unpublished data).

ICI is in a position to authorise the use of the unpublished data referred to. The additional references cited are :

Wilkinson, W. (1980)
PARAQUAT AND DIQUAT : Longterm high rate trial, Frensham UK.
1. Management of site, effects on crops and weeds and residues in crops.
ICI unpublished report RJ0013B.

Gowman, M.E, Riley, D., Newby, S.E. (1980)
PARAQUAT AND DIQUAT : Longterm high rate trial, Frensham UK.
2. Persistence and movement in soil and glasshouse bioassay.
ICI unpublished report RJ0014B.

Riley, D. (1981)
The fate and effect of paraquat and diquat residues in soil.
Proceedings for the National Spray Seed Conference 1981, Albury, New South Wales, Australia.

/....

Hance, R.J. et al (1980)
Apparent decomposition of paraquat in soil.
Soil Bio. Biochem. 12; 447-448.

Page 21, lines 24-31. May we propose an alternative text?

Although, as mentioned, adsorption to clay is important, extremely sandy soils can adsorb and inactivate significant quantities of the herbicide, as illustrated by studies on a South African vineyard soil that contained only 1% clay (Riley et al, 1976). Over an 8-year period over 20 applications (total 15.6 kg paraquat/ha) resulted in saturation of about 20% of the soil paraquat strong adsorption capacity in the top 2.5 cm. The paraquat residues were not phytotoxic in the field or in the greenhouse tests with different plants. No paraquat residues were detected (<0.05, <0.03, <0.03 micrograms/g) in leaves, grapes and twigs, respectively.

Page 21, lines 32-37. May we propose an improved construction?

Very low concentrations of free paraquat would be detected easily by their phytotoxicity. Five trials at four sites were conducted by Newman and Wilkinson (1971). In four of the trials, there were single applications of paraquat at 112 kg/ha at sites subjected to normal agricultural practice. At this unrealistic, extremely high rate, short-duration residual phytotoxicity was observed. On undisturbed plots of mineral soils, seedlings did not appear for ....

Page 22, line 8. "a gross overdose".

Page 23, line 23. The statement "No residues were detected" is of very limited value unless the limit of detection is quoted. That limit was 0.01 ppm.

Page 24, line 4. Exposure to paraquat by the air is NOT important in spraying and harvesting operations. Dermal is the principal route of occupational exposure. Supportive references are :

Chester, G. and Ward, R.J. (1981)
"Paraquat - Occupational Exposure and Drift Hazard Evaluation During Aerial Application To Cotton In California USA." ICI Central Toxicology Laboratory report no CTL/P//581 (unpublished).

Chester and Woollen, 1982 - already cited.
Hogarty, 1976. Reference supplied separately to IPCS.
Staiff et al, 1975 - already cited.

Page 24, line 12. The correct units are mg/hr.

/....

Page 24, lines 17-18. The paper written by Seiber and Woodrow, 1981, refers to the collection of particles by a cascade impactor placed at three points downwind of the spraying. The position of these cascade impactors is not clear from the paper, but at these points 55% of the droplets drifting had a mean particle diameter of 12 microns and 45% had a mean particle diameter of less than 4 microns.

Page 24, line 22. "... mean total respiratory exposure ...."

Page 24, line 24. 1982.

Page 26, line 16. We are surprised that no reference is made to the substantial evaluations of the 1970, 1972 and 1981 JMPRs.

Page 26, lines 24-25. The sentence does not seem to make good scientific sense and is best deleted, we believe.

Page 27, line 12 to page 28, line 7. The fate of paraquat in large animals is addressed far more completely in the Evaluations of the 1976 JMPR, pages 475-480 and page 483. We recommend the use of that text, deleting reference to ICI unpublished data not submitted to IPCS and citing instead the 1976 Evaluations.

5. Biological Activity Of Residues

Page 28, line 24. We suggest deleting "Wilkinson (1971)" - see Appendix I.

Page 28, line 35. "Knight and Baldwin (1970)" is not shown in the references list and is best deleted, we propose. For "Gratton (1970)" read "Riley et al (1976)" - see Appendix I.

Page 28, lines 11-12. For "(Austin and Calderbank, 1964)" read "Calderbank and Slade, 1976" - see Appendix I.

6. Toxicokinetics, Metabolism and Mechanism Of Action

Page 29. Additional data are required in the Evaluations of the 1976 JMPR, pages 471-2. Reference to ICI unpublished data which have not been submitted to IPCS should, we recommend, be replaced by citing the 1976 Evaluations.

Page 29, line 32. Litchfield et al (1973). The Conning paper does not appear in the references list.

Page 30, lines 17-20. We propose a replacement text :

/....

Paraquat absorption through animal and human skin has been studied using an in vitro technique (Walker et al 1983). Human skin was shown to be very impermeable to paraquat, having a very low permeability constant of 0.73. Furthermore human skin was found to be least 40 times less permeable than animal skins tested (including rat, rabbit and guinea pig). Hence animal dermal toxicity studies will tend to overestimate the potential risk of paraquat poisoning to man via this route of absorption.

Reference : Walker, M., Dugard, P.H., and Scott, R.C. (1983)
Absorption through human and laboratory animal skins : in vitro comparison.
Acta Pharma Suecica - 20 1 p52-53.

Page 33, line 34. "1 hour" should read "17 hours".

Page 33, line 38. The paper of Saito et al, 1979, does not appear in the references list.

Page 35. Since the heading for 6.2 relates to observations we believe that "Experience In Humans" would be a better heading than "Human Studies", which has unfortunate connotations in this particular context.

Page 35, line 11. First day (not list).

Page 35, line 27. The unit is mg.

Page 35, line 32. For "Figure 4" read "Figure 6".

7. Effects On Animals

Pages 39 to 44. The text is particularly weighty in relation to the remainder of the document.

Page 45, line 34. For "(McElligott 1966)" read "(FAO/WHO 1973)", relating to the Evaluations of the 1972 JMPR - see Appendix I.

Page 46, line 2. For "(Fletcher et al 1972)" read as in the preceeding comment - see Appendix I.

Page 47, line 19 and page 51. "(Fletcher et al, 1972a)" read as in the preceeding comment - see Appendix I.

Page 47, lines 31 - end. May we respectfully suggest that this is a trivial paper in relation to the assessment of real health risks due to paraquat? We recommend that the paragraph be deleted.

Page 48, line 1. There is no Section 5.4 in the present draft.

Page 49. The figure for man should not appear as an oral LD50. References f and k do not appear in the table.

/....

Page 52, line 11. May we recommend an addition?

More recently, Okonek et al have shown that activated charcoal can be as effective as Fullers Earth or bentonite in the treatment of paraquat poisoning.

Reference : Klin. Wochenschr. (1982) 60 207-210
Okonek, S., Setyadharma, H., Borchert, A. and Kriehke, E.G.

Page 53, lines 5-9 and Table 14. The text is not comprehensive and in any case contributes little. May we propose a re-wording, based in principle upon current works?

The first fatalities from oral acute paraquat poisoning occurred in 1964 (Bullivant, 1966). The earlier cases ... (lines 10-13)... bottles. Stricter official control and greater public awareness have resulted in a lower ....
(line 14 to end of paragraph).

Page 54, line 4. We propose an addition :

More recently Bramley and Hart showed that 95% of fatalities are due to suicides.

Reference : Paraquat Poisoning in the United Kingdom
Bramley, A. and Hart, T.B.
Human Toxicology 2 (2) 417 (1983).

Page 54, lines 14-17. Instead of citing the case described in Kimura et al 1980, it would be more representative to describe the case of Jaros et al. The reasons for the proposed change are as follows :-

i) The section refers to poisoning via the skin, yet Kimura et al appear to describe a case of poisoning by ingestion.

ii) The features of the poisoning are not at all consistent with paraquat poisoning. Tetanus is not a physical sign associated with paraquat poisoning. The description of this case will therefore tend to confuse readers as to how paraquat poisoning actually presents clinically. Instead it would be more appropriate to use the paper by Jaros et al (1978) which is already cited in the draft.

We suggest the following wording :

In another report, a 44 year old man sprayed a paraquat spray solution of 4% w/v paraquat ion, ie about 10 times the maximum recommended spray concentration. The spray solution leaked from his sprayer onto his neck, back and down to the perineum over a period of several hours. The skin of that region subsequently became inflamed and necrotic and eventually he died of paraquat poisoning thirteen days after the incident.

/....

Page 55, lines 14-19. We would like to propose detailed changes to the draft text which we consider important :

Symptoms of poisoning depend upon the dose absorbed. It is difficult to estimate the dose absorbed from the case histories since in many cases the patients spat out part of the paraquat concentrate or vomited profusely after swallowing the herbicide. Some patients have survived after apparently ingesting 50-100 ml GRAMOXONE (10-20 g paraquat) whereas some died after taking as little as two sachets of WEEDOL (2.5 g paraquat).

Page 55, line 22. The unit is incorrect. (g)

Page 56, lines 3-4. The current text is not representative. Patients develop oropharyngeal ulcerations usually within 24 hours.

Page 56, line 9. We do not consider the reference to chest pain representative and so recommend its deletion.

Page 58, Section 8.1.6.7. Two other cases referring to the effect of paraquat on the human foetus have been reported in the literature (Fennelly et al 1968, Musson and Porter 1982). In the case described by Fennelly, a married woman drank paraquat, when she was 28 weeks pregnant. Although the women eventually died of paraquat poisoning there were no abnormal pathological findings in the foetus on autopsy.

The other case involved a woman who drank a small amount of paraquat, when 20 weeks pregnant (Musson and Porter). She survived the poisoning, giving birth to a normal baby, who was assessed until the age of 3 years, during which time the child underwent normal development.

References : 1. Fenelly et al. B.M.J. 3 722-723 (1968)
Paraquat poisoning in a pregnant woman.

2. Musson and Porter. Postgraduate Med. Journal (1982) 58 731-2
Effect of ingestion of paraquat on a 20-week gestation fetus.

Page 59, line 8. You may wish to make an addition regarding the emetic, particularly since that is mentioned on page 53.

Evaluation of the effectiveness of an emetic addition to paraquat formulations in cases of human poisoning has so far proved difficult. Nevertheless such an addition has been shown to increase the incidence of early spontaneous vomiting, when paraquat formulations containing emetic have been swallowed.

Reference : Paraquat poisoning in the United Kingdom
Bramely, A. and Hart, T.B.
Human toxicology Vol 2 No. 2 417

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Page 60, Section 8.2. It may be a more comprehensive and logical sequence to start with 8.2.1.1 Exposure to Agricultural Workers and 8.2.1.2 Epidemiological Studies and Case Reports.

8.2.1.1 Exposure to Agricultural Workers

Several studies have been undertaken assessing dermal and inhalational exposure to agricultural workers spraying paraquat by various methods. The current wording "only a few surveys" is a misrepresentation of the extent of available data, particularly when judged in context of data available on other pesticides. The results of these studies are summarised in the following table.

| Application Method | Dermal Exposure (mg/hr) | Total Respiratory Exposure (mg/hr) |
|---|---|---|
| Hand-held knapsack (Chester and Woollen 1982) | 66 (12.1-169.8) | $(0.45\text{-}1.3) \times 10^{-3}$ |
| Vehicle mounted (Staiff et al 1975) | 0.4 (0.1-3.4) | $0\text{-}2 \times 10^{-3}$ |
| Aerial - a) Flagger | 0.1-2.4 | $0\text{-}47 \times 10^{-3}$ |
| b) Pilot | 0.5-0.1 | $0\text{-}0.6 \times 10^{-3}$ |
| c) Mixer/ loader | 0.18 | $1.3\text{-}1.5 \times 10^{-3}$ |
| (Chester and Ward, 1981) | | |

Two conclusions are evident from the above table :

i) The main route of exposure of agricultural workers to paraquat is to the skin, respiratory exposure is negligible.

ii) Potentially the worst case exposure situation is via knapsack spraying.

It is therefore important to understand how significant is paraquat penetration through human skin (see page 30 - dermal absorption) when considering the safety in use of paraquat. As, potentially, the worst case exposure results from knapsack spraying, it follows that if this method is safe to use with paraquat, then the other methods must be safe also.

If our proposals are accepted then it would become necessary under

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8.2.1.2 - Epidemiological Studies - Agricultural Workers to delete references to Chester and Woollen (1982), Staiff et al (1975) and Seiber and Woodrow (1981) as these are now covered by Section 8.2.1.1

The first paragraph under 8.2.2 should then read

Paraquat has been in agricultural use since the early 1960's and several studies have been conducted on spray operators. Most of these studies refer to the relatively short term effects from exposure to paraquat (Swan 1969, Hearn and Keir 1971, Makovskii 1972, Hargarty, C. 1976). Howard (1981) has also studied the health of sprayworkers associated with exposure to paraquat over longer period of time.

One would delete lines 30-40 on page 61 and on page 62 lines 0-6, 13-14 and 29-34 since these would have been included in Section 8.2.1.1, under our proposals.

Page 61, line 5. May we propose :

"The potential risk of dermal exposure."

Page 62, lines 26-34. The work of Howard (1980) is most valuable in relation to assessing the long term safety to spray operators rather than of formulation workers and therefore it should precede the sub-section on 'formulation workers', in our view. Given also that, under our proposals, lines 29-34 would have been covered in the suggestions for 8.2.1.1, we would re-write lines 26-28 as follows :

The potential long term hazard associated with the use of paraquat has also been studied. Howard et al (1981) studied the health of 27 spraymen who had been exposed to paraquat for an average of 5.3 years, and compared them with two non-exposed control groups consisting of 24 general workers and 23 factory workers. The workers were given full clinical examinations and tests of lung, liver and kidney function were done. There were no significant differences in all health parameters measured between the groups, indicating that long term use of paraquat is not associated with harmful effects on health.

Page 62, line 19. We believe "2.3" years should read "5.3" years.

Page 63, lines 1-7. We recommend considerable care over the use of the Fitzgerald data. May we propose an alternative text?

It should be emphasised that carelessness in handling paraquat may have serious consequences. The available evidence indicates that, at the recommended dilution rates and correctly used, paraquat does not cause systemic oral, inhalational or dermal effects. Skin and eye irritations have occurred only when protective measures were disregarded, notably when handling liquid concentrates.

/....

Two reviews have also been published in the literature by Howard (1980) and Garnier, R. et al (1980). Both reviews conclude that paraquat is safe to use, provided that the manufacturers recommendations are followed and that the main side effects from occupational use are local and relate to the caustic nature of the product.

Reference : Garnier, R. et al (1980) : Toxicity of paraquat when used for occupational purposes. Med Leg Toxicolog 23 3 131 - 141.

Page 63, lines 10-11 and 16-18. While we in no way condone the practice of operators sucking or blowing out nozzles or smoking while spraying, it also needs to be stressed that spray-diluted paraquat normally contains 1-2 g paraquat ion per litre of fluid (maximum 5 g/litre). If the minimum potential oral lethal dose of paraquat in man is 2-5 g paraquat ion, then someone sucking or blowing on a nozzle would have to drink 1-2 litres of spray solution, before they had swallowed anywhere near a lethal dose. The practice of sucking or blowing out nozzles is not to be condoned but it is not likely to be a dangerous practice.

Similarly smoking with paraquat contaminated hands is not to be condoned, but it is virtually impossible to get a lethal or near-lethal dose by this means. The case described by Mourin 1967, is likely to have been swallowing concentrate and to disguise the fact, the patient will undoubtedly have claimed that it was from smoking a cigarette with contaminated hands.

We feel rather strongly that the draft text should be modified to take these remarks into account.

Page 63, lines 29-37. Severe skin damage was not present in the case described by Newhouse et al (1978). The woman had scratches on her arms and legs. It seems probable that she died from paraquat poisoning, but there was no confirmation of this. Furthermore, the evidence that significant skin absorption of paraquat had taken place was extremely flimsy. There was more evidence to suggest that oral intake was the route as the woman had complained of nausea and vomiting, features suggestive of paraquat ingestion. The authors themselves believe that their case is speculative; they state this in the discussion section and we therefore feel strongly that the final text of the IPCS review should reflect that point.

Page 64, line 36 - end. We recommend :

them to be well below the TLV. There have been some reports (Malone et al, 1971; Mircev, 1976; George and Headworth-Whitty, 1980) of non-fatal toxicity as a result of inhalational exposure but some doubt must always remain as to the validity of such anecdotal reports (Hart 1980).

Reference : Hart, T.B. (1980)
Non-fatal lung disease due to inhalation of nebulised paraquat
B.M.J. 281, 63-64.

/....

9. Evaluation Of Health Risks To Man

Page 65, lines 11-13 and 16-19. May we recommend re-wordings to be consistent with our earlier comments?

(11-13) the soil is insignificant in comparison with adsorption to clay particles. Micro-organisms can degrade free paraquat rapidly but chemical degradation of adsorbed paraquat is relatively slow.

(16-19) metabolic or breakdown products are to be expected (Sections 4.3 and 5.1). While strongly-bound inactive paraquat is persistent in the soil, longterm field studies have shown degradation rates of 5-10% per annum which is sufficient to prevent saturation of soil deactivation capacities. At normal

Page 65, lines 22-24. May we suggest a minor wording improvement?

... less than 2 weeks (Section 4.3.2). at which level phytotoxic damage... is unlikely to occur. When applied before there is .....

Page 66, line 6. We recommend

concentrates in small unlabelled household bottles which can also be accessible to children. While the suicidal use of paraquat is difficult to control, strict rules on the labelling and safe use of paraquat have been effective in limiting instances of accidental ingestion.

Page 66 line 13. We think it should be stressed that the principal route of occupational exposure to paraquat is dermal.

Page 66, lines 22-23. We refer to our earlier remarks that, while we do not condone the practice in any way, neither is it correct to imply that dangerous oral exposure occurs when blowing out nozzles.

Page 66, line 25. We consider the following wording preferable :

... good personal hygiene and proper adherence

Page 66, lines 29-31. At recommended use concentrations, lethal quantities will only be absorbed via the skin if extensive skin damage has first been allowed to occur. Our earlier contributions are relevant. Thus we think this should be made clear.

Page 67, lines 5 and 24. The document contradicts itself on the same page. The correct value, for the dichloride, is the one shown in line 5.

Page 67, Table 17. Reference to all the MRLs recommended by th JMPR in 1970, 1972, 1976 and 1981 would be appropriate.

Page 68, lines 3-5. While we feel sure that it was unintended the current text is capable of being misunderstood. The poisonings among the general populations derive from gross mis-use as do the very few reported cases of death in occupational exposure. To eliminate the potential for misunderstanding may we propose :

/....

While there is no hazard to operators during the normal recommended uses of the product, experiences of mis-use of paraquat in practice stress the value of effective regulations which limit the availability of the 20% liquid products to qualified personnel.

May we now come back to our comments on the SUMMARY which we think are especially important, partially because the current draft does not, in our view, properly represent the balance of what follows in the main text and partially because we anticipate that certain readers will limit their attention to the summary. Our comments on the summary will also reflect our comments on the main text (above).

Page 6, lines 9-10. Paraquat is most commonly used as the dichloride, not the di(methylsulphate) salt.

The unqualified statement "May decompose on heating, giving rise to toxic decomposition products" is, we believe, misleading. We recommend limiting remarks to the ionic, water-soluble, non-volatile nature of paraquat, which are key points.

Page 7, lines 11-12. We suggest :

Although the rate of absorption will increase if the skin has been damaged, paraquat is absorbed very poorly through normal human skin.

Page 7, lines 32-33. May we suggest that the references to selenium- and vitamin E deficient diets in the summary is quite irrelevant. While the addition of "or activated charcoal" would be beneficial after "administered clay".

Page 8, line 4. In our experience, only lethal dosages have produced the functional changes listed.

Page 8, lines 10-11. The summary of the mutagenicity fails to capture the tone of the summing-up on page 47, line 10.

Page 8, lines 12-13. We commented in the main text that the work on methane-induced tumours had no real bearing upon an assessment of health risks due to paraquat. The reference to it in the summary really is totally misplaced, may respectfully suggest.

Page 8, line 17. The number of cases of suicidal poisoning is large. The number of accidental cases is small and is remaining so following the various measures cited. However, it would be quite wrong to leave the impression that the measures have caused a decline in the number of suicide deaths, in our experience.

Page 8, line 22. The unqualified sentence "Granules are safer" could be taken to imply "in normal use". There is no reason to suggest that the 20% liquid is not safe in normal use. Therefore may we propose

Granules are safer where a significant potential exists for mis-use.

/...

Page 8, line 38. Paraquat levels in plasma will normally provide the best indication of prognosis.

Page 9 Occupational Exposure. We believe it would be more representative to put

Occupational exposures do not pose a hazard under normal conditions of use, when the label recommendations are followed. This has been shown by several studies in which the potential risk which may be associated with paraquat exposure, either short or long term, was estimated. Minor side effects such as nail damage, delayed skin healing and occular effects have been described as resulting from exposure to paraquat.

There has been a small number of mainly anecdotal cases of paraquat poisoning reported in the literature, allegedly resulting from dermal exposure. Prolonged contact with high concentration paraquat solutions, leading to extensive and severe skin damage, with loss of barrier function, and leading to enhanced dermal absorption of paraquat, is necessary for deaths to result from dermal exposure.

Copies of unpublished ICI reports which we have introduced in our comments are being sent to you under separate cover.

We thank you again for the opportunity of comment and wish your team a successful and productive meeting during the week of 5 December.

Yours sincerely

R. D. Wiseman

G A Willis
p.p. Product Safety & Registration Group

Enc

APPENDIX I

Suggested Changes in Referencing

1. Austin, W.G.L. and Calderbank, A. (1964) (ICI unpublished data).

   It is suggested that this be replaced by Calderbank (1968), a published review which is already cited.

2. Baldwin, B.C. (1970) (ICI unpublished data)

   The technical position is encompassed within the paper of Riley, D., Wilkinson, W. and Tucker, B.V. (1976) which is already cited as a published reference.

3. Baldwin, B.C. and Griggs, R.E. (1971) (ICI unpublished data)

   This work is reviewed in the published review of Calderbank, A, and Slade, P. (1976) which is already cited.

4. Broadhurst, T.O., Griffiths, D. and Mc Elligott, T.F. (1966) (ICI unpublished data)

   This work is reviewed in the 1970 Evaluations of the JMPR.

5. Clark, D.G. (1965) (ICI unpublished data)

   This work is reviewed in the 1970 Evaluations of the JMPR.

6. Daniel, J.M., Edwards, M.J., Slade, P. and Walker, G.H. (1971) (ICI unpublished data)

   This work is reviewed in the 1976 Evaluations of the JMPR.

7. Fletcher, K., Herring, C. and Robinson, V.M. (1972) (ICI unpublished data)

   This work is reviewed in the 1972 Evaluations of the JMPR.

8. Fletcher, K., Flegg, R. and Kinch, D.A. (1972a) (ICI unpublished data)

   This work is reviewed in the 1972 Evaluations of the JMPR.

9. Gage, J.C. (1969) (ICI unpublished data)

   This document has not been reviewed in the open literature hitherto. ICI agreed to IPCS citing this proprietary information.

10. Gratton, R.P. (1970) (ICI unpublished data)

    The technical position is encompassed within the paper of Riley, D., Wilkinson, W. and Tucker, B.V. (1976) which is already cited as a published reference.

11. ICI Ltd (1972) (Residue Method PPRAM-3)

    This is freely available on request from ICI and is not deemed to be proprietary data.

12. ICI Ltd (1978) (ICI unpublished data)

The document is marked "highly confidential". ICI does not consider the contents most appropriate to an IPCS review and is not prepared to give its permission to an authorised use of the document.

13. McElligott, J.F. (1966) (ICI unpublished data)

The work is reviewed in the 1972 Evaluations of the JMPR.

14. Newman, J.F. and Wilkinson, W.W. (1971) (ICI unpublished data)

The document has not been reviewed in the open literature hitherto. ICI agrees to IPCS citing this proprietary information.

15. Tucker, B.V. (1969) (Chevron Chemical Co unpublished data)

Has Chevron Chemical Co given permission for this use of its data? If not, it can be noted that the work is encompassed within the paper of Riley, D., Wilkinson, W. and Tucker, B.V. (1976) which is alredy cited as a published reference.

16. Wilkinson, W. (1971) (ICI unpublished data)

The work is encompassed within the paper of Riley, D., Wilkinson, W., and Tucker, B.V. (1976) which is already cited as a published reference.