WHAT IS THE HUMAN MLD FOR PARAQUAT

SUMMARY

Why need to clarify dose?

The basis for classification and labelling schemes is to compare toxicities of products under similar conditions, allowing products to be classed and ranked. Thus, as with all other chemicals, classification and labelling for paraquat and its formulations is based on rat data where we have a wealth of data generated under controlled experimental conditions giving a reliable and consistent reference point eg

Homogenous population
Known genetic variability
Good health status
Same weight range and age
Nutritional status known (eg fasted/non fasted)
Known dose

Paraquat has been extensively tested and from studies in different species, we know that paraquat plasma levels at MLD doses are similar, but that there are differences in the actual MLD doses. (note – these types of data are often not available for other compounds). This knowledge has led some authorities, and authors of published literature, to suggest that these species differences should be taken into consideration in the classification and labelling of paraquat and formulations. However, the difficulty arises that these studies (in other species) are often not well controlled and therefore the MLDs will have large margins of error.

To have an appreciation of the MLD for humans is of obvious interest, especially to medics who need to predict the likely consequences for patients who present after having taken an oral dose of paraquat. There are many confounding factors in the deliniation of the human MLD, thus it is stressed that a more reliable indicator of outcome for the patient is a measure of plasma or urine paraquat concentration (Appendix 1). Irrespective of this, we need to try and construct a dose/concentration and survival curve to assist in these predictions and to counter speculation in the literature.

This document briefly reviews the key documents/references relating to human MLDs and highlights the practical challenges in defining a precise value for this.

Our objective should be to establish
- A dose (mg/kg) response curve
- the largest dose that can reasonably be considered not to result in death in the majority of cases (and which would have no long term consequences)
- the smallest dose that can reasonably be considered to cause death in the majority of cases

o based on these, a median lethal dose

Challenges in defining the human MLD dose

- o The toxicity of pq is expressed as a function of dose and time ... the larger the dose, the shorter the period to death and the lower the prospect for survival irrespective of treatment. A smaller dose (especially if not treated) can still be fatal over a longer period of time

- o Are we therefore trying to define a dose *that if not treated* will result in 50% mortality OR a dose, *irrespective of treatment* that meets this criterion? OR are we trying to understand the dose-response relationship, irrespective of the impact of treatment?

- o There is often lack of clarity on which product has been used – important in defining paraquat ion concentration; also, if the product is a generic, we need to know if it contains emetic.

- o Similarly, bodywt is often not recorded and therefore we have to estimate wts for different ages (but often not for ethnicity or sex .. eg, a 40 yr western male is likely to have a much larger body mass than say a 40 yr Asian female worker

- o How much product has been consumed? This is hardly ever described in terms of mls, but more often as a sip/mouthful/cupful – which leads to potential miscalculations. Also important to know how much, if any, has been regurgitated (is it possible to estimated the amount of product/paraquat in the vomitus?)

- o Different treatment regimes may/will have an impact on the survival of patients, particularly at or around the MLD – therefore any MLD figure that is determined will inevitably have large margins of error associated with it.

- o Many different factors associated with the life-style/ health status of the individual may impact on survivability eg

  - o was alcohol consumed at the time of the time of the suicide (could influence absorption)
  - o was the stomach full or empty (binding of cation to food particles)
  - o health status (smoker / asthmatic/ renal and hepatic status etc); presence of gastric ulcers

- o These influencing factors highlight the need to get back to the raw data (where/if it exists) to clarify assumptions made.

Published Literature – reporting of MLDs

A figure of 40mg cation /kg is a value often cited in the literature associated with human toxicity – this is *not* considered a human MLD, but a dose at which survival is unlikely and will usually result in death in a few days. Where does this value come from and how reliable/consistent is the value? What is the shape of the dose response curve? For the reasons explained above, as discussed above, it is imperative that to validate the data presented in papers we have access to individual case histories to ascertain doses, bodywts, health status etc. We do not have these data.

40mg ion/kg = 3g/70kg bodywt = 15ml of a 20% ion solution of Gramoxone

A list of some of the key publications is given in Appendix 2.

It is interesting that the usually quoted ranges for toxicity of <20, 20-40 and >40 mg/kg were set back in 1987 and these data seem to have become fixed and almost "folk-lore" in being re-iterated in subsequent publications – possibly/probably without further reference back to raw data to substantiate the claims. Additionally, the safening agents, in particular the emetic, was introduced only in the early 1980s, so it could be questioned whether the quoted toxicity ranges take this into account – or if the data set contains both emetic and non-emetic cases.

Conclusions from published literature

- o The data quoted in the literature are reasonably consistent, though this may be because they have been cited from an original paper

  - o a dose greater than 40mg pq ion/kg will result in death within a few hours or days
  - o 20-40mg/kg will likely result in death, sometimes within 24 h, but usually within 2 weeks
  - o a dose of less than 20mg/kg is likely to be asymptomatic, or result in gastrointestinal effects or transient lung effects.

- o It can be assumed from these data there is thus a steep dose response curve around a dose of 20-30mg/kg.

- o Sato cites a case where a dose of 4mg/kg has caused death of the patient; this appears outside of the standard data set

Positions on human MLD cited by Syngenta

A list of the key activities/publications is given in Appendix 2.

There are some minor inconsistencies in the data presented in the treatment handbook compared to the Lock and Wilks chapter, with the latter indicating wider bands for the different classes of toxicity. The latter wider bands are borne out by the data from the MgSO4 trial where there was survival above the 3g paraquat (40mg/kg) that is assumed to invariably result in death.

As with the published data, there is the dilemma that bodywts do not appear to have been recorded and thus these banding are imprecise.

It is recommended that the data from the MgSO4 trail and the Japanese Ian Pate analysis are revisited to see if further information can be gleaned and combined to improve our data set.

Additionally, the forth coming Sri Lanka study offers a unique opportunity to gather these data and to closely consider the impact of health status on the data.

Conclusions/recommendations for further analysis

o   Based on the existing data sets/literature references it is imprecise to quote a human MLD for humans due to the nature of the incidences, paucity in estimating dose receieved etc, and in lack of compensation for factors such as food intake, health status, ethnicity, metabolic state etc.

o   Plasma and urine paraquat concentrations remain the most accurate predictors for the outcome of patients.

o   There is reasonable consistency in the published literature that
  - o   a dose greater than 40mg pq ion/kg will result in death within a few hours or days
  - o   20-40mg/kg will likely result in death, sometimes within 24 h, but usually within 2 weeks
  - o   a dose of less than 20mg/kg is likely to be asymptomatic, or result in gastrointestinal effects or transient lung effects.
  - o   The published data therefore suggest a steep dose response curve around a dose of 20-30mg/kg.
  - o   Care should be taken with the published data – the toxicity classes are probably just repetition from the first Merideth and Vale paper

o   The internal Syngenta data suggests the doses in the literature may be on the low side (eg from the MgSO4 trial patients where there was survival above the 3g paraquat (40mg/kg) that is assumed to invariably result in death).

o   It is recommend that the Japanese data and MgSO4 data are revisited to see if we can assign bodywts to the patients and assess health status that may have influenced the toxic dose ; the data can then be combined to increase the accuracy

o   Further data should be gathered from the Sri Lanka trial

o   With the existing data we should consider
  - o   the largest dose that can reasonably be considered to not result in death in the majority of cases (20 – 25??)
  - o   the smallest dose that can reasonably be considered to cause death in the majority of cases (25-30??)
  - o   determine a median lethal dose

APPENDIX 1

Use of Plasma Analysis in determining Dose

The difficulties in determining the exact does received by patients, for the reasons stated above, has lead to the measurement of paraquat plasma concentration to be used as an indicator of prognosis. Proudfoot et al (1979) found that patients whose plasma paraquat concentration did not exceed 2.0, 0.6, 0.3, 0.16, 0.1 mg/l at 4, 6, 10, 16 and 24 after ingestion survived. Hart et al e and subsequently Sawda et al extended this work to denote the plasma paraquat concentration that would predict 50% survival and a severity index for paraquat poisoning .

APPENDIX 2

INFORMATION ON HUMAN MLD FROM PUBLISHED LITERATURE

Vale, Meredith and Buckley 1987 (H Tox 6 41-47)
- Reviewed 150 patients and categorised outcome into 3 grps
  - >40mg/kg as a fulminant dose (equivalent to >15ml Gramoxone)
  - 20-40 mg/kg as moderate to severe (>1 sachet of Weedol or < 15ml of 20% Gramoxone). Death occurs in the majority of cases but may be delayed for 2-3 weeks.
  - <20mg/kg bdywt. Mild poisoning , < 1 sachet Weedol. Full recovery would be expected.

Bismuth, Scherrmann, Garnier, Baud and Pontal 1987 (H Tox 6 63-67)
- lethal concentrations may be achieved within 6h of ingestion of 35mg/kg.
- Renal failure can occur when dose of 20mg/kg has been ingested; when patients show renal failure, 19 0f 20 patients died.

ICPS (JMPR WHO/FAO) 1987 EHC Monograph #39
- cites a *minimum* human oral lethal dose of approximately 35mg/kg bodywt,, based on literature reviews of Pederson et al 1981 and Bismuth et al 1982.
- Some patients survived after ingesting 50 – 100ml Gramoxone (10 – 20g pq ion; approx 140 – 280mg/kg bdywt) whilst there are reports of deaths from ingesting 2 sachets of Weedol (2.5g pq ion)

Pond SM 1990 (Med J Australia 152 256-259)
- Between 25% and 75% of patients who ingest paraquat liquid concentrate die
- LD50 in the adult human is 3-5g; thus ingestion of 10-15ml of the 20% concentrate can be fatal. Patents can easily ingest many times an oral LD50 dose.
  - 15ml of 20% concentrate (>40mg/kg) usually die within a few hours to days
  - 20-40 mg/kg usually leads to pulmonary fibrosis after a few days and up to several weeks later.
  - Ingestion of < 20mg/kg will result in only mild toxicity or be asymptomatic. Toxicity is usually limited to the gi tract although transient abnormalities in gas transfer and vital capacity may be detected.

Winchester 1995 (in Paraquat Poisoning)
- Ingestion of a massive dose (>30mg/kg or 50ml of paraquat concentrate) results in death within several hours to a few days.
- Ingestion of 4ml/kg caused similar symptoms and acute renal failure, sometimes within 24h

EPA Treatment Handbook for Pesticide Poisoning <mark>(need reference and correct title)</mark>

- The summary states that the LD50 in humans I approximately 3-5mg/kg which translates into 10-15ml of a 20% solution. *This is clearly at odds with the wealth of other literature and can be assumed to be an error.* Further in the text, more recognised values are presented:
- >40mg ion/kg (more than 15ml of a 20% soln) – mortality is essentially 100% in 1-7 days
- 20-40mg/kg – death occurs in most cases, but may be delayed 2-3 weeks.
- <20mg/kg – no symptoms or only gi symptoms occur. Recovery is likely.

Bismuth C, Hall A and Wong A 1995 (in Paraquat Poisoning) 1995

- Hyperacute >55mg/kg. Patients survive for less than 4 days
- Acute 30-50mg/kg (equivalent to a single swallow of 12-20% concentrate product)
- Subacute <30mg/kg benign intoxication; gi insult is usually moderate
- Minimum fatal dose is 20-40mg/kg. One swallow of 20g/l (note error) concentrated commercial formulation is thus sufficient to result in death.
- Doses of 40 and 50 mg/kg results in classical pulmonary fibrosis and death is late
- >55mg/kg, patients die within the first 4 days

Sats S 1995 (in Paraquat Poisoning)

- minimum lethal dose is approx. 35mg/kg, though as little as 4mg/kg can be fatal.
- Quotes Vale data for mild (<20); moderate to severe (20-40) ; and fulminant (>40).

Garbino P 1995 (in Paraquat Poisoning)

- A = 50mg/kg is fatal within 72 hours
- < one mouthful (20-50 mg/kg) can cause lethality up to 70 days following ingestion

APPENDIX 3

References for Syngenta Positions on Human MLD

Treatment Booklet: 1985 through to 2002
- o The 1985 booklet did not give doses in mg/kg; it states that an oral dose of about 3g is likely to be fatal, if untreated, to an adult. 3g is contained in 15ml Gramoxone or in 1.5 sachets of Weedol or Pathclear
- o In the 2000 and 2002 booklets it is stated;
  - o 40mg/kg is a fulminant dose (sudden/intense/severe/rapid) – which I take to infer is likely to be a dose that is always fatal
  - o 20 – 40mg ion/kg is a dose "where survival is possible in some case". Death occurs 2-3 weeks later in the majority of cases.
  - o <20 mg/kg is a dose where complete recovery would be expected.

Lock and Wilks 2000? (Handbook of Toxicology p 1559 – 1603)
- o Mild or sub acute poisoning is defined as ingestion less than 20 – 30 mg/kg and this rarely has serious consequences. (The smallest fatal dose is given as 16.7mg/kg, though this is from a Weedol incident, thus the total bipyridyl content would have been 35mg ion/kg.)
- o Moderate to severe acute poisoning occurs when ingestion is >20 – 30 mg ion/kg but < 40 – 50mg/kg. In most cases, deaths will occur over a period of 5 days.
- o Fulminant or Hyperacute Poisoning occurs following ingestion of >40 – 55mg/kg and patients usually die within 4 days. There are 52 cases in the literature where patients have survived following a dose reportedly well in excess of 55mg/kg (and, in one case, >200mg/kg)

Jon Heylings (memo June 1991, updated June 1997)
- o 69 human paraquat cases (from the Ohno 1987 Japanese data set) were examined and a dose response curve plotted with band widths of 1.5g pq ion. There was a steep dose response between half (0.5) and x2 the lethal dose. The median lethal dose was calculated as 3.1g (The average suicide patient will ingest approx 7-10g (ie x 2 - 3 the MLD).
- o Note: CTL/R/1250 is not indexed or held within the CTL Archives.

Ian Pate Review of Human Poisonings to determines a MLD and survival rates
- o This analysis used data from ICI Japan (1979 – 1985); Ohno data (1985 and 1986-7) and from Crete (date not known). There were a total of 465 cases. This is thus an extension on the Heylings report
- o It was concluded that the median amount of parauqat ingested was 9.6g from the ICI Japan data, and 6g from the Ohno 1986 – 1987 data. Crete data showed a median ingestion of 7 g. the review ie dose rates are 2-3x that usually quoted as the MLD of 3g per person. The Ohno (1985) data showed a much higher value of 20g. The overall median ingestion rate from these data was 10g. A previous review of ingestion rates (CTL/R/1250) quoted typical ingestion rates of 30-60g which Pate considers clearly an over-estimate of the true median.

- o There was a 75% mortality rate from these data and the median lethal dose was approx. 3g. Earlier data sets (I assume R/1250) gave slightly higher mortality rates for intakes of less than 1.5g with no obvious trend within the 0 – 1.5g interval.
- o Comments on data set:
  - o The age of the datasets could indicate a mix of emeticised and non-emeticised cases
  - o Bodywts were not tabulated – need to check if these data are available. We have age of patient, and for the 1985 Ohno data, gender. Some estimates of weight would be possible.
  - o Recommendation – review this data set to assess feasibility of constructing dose/response curve.

Mitchell/Scott/Middleton

A review of the literature on survivors of paraquat poisoning was commissioned in Sept 1994 and updated in 1996 and 1997. Assumptions were made on bodywt in relation to age; volumes for mouthfuls/sips etc and on %pq ion in products (default = Gramoxone). The aim of the exercise was to refute the comment (from a regulator) that a dose of 20-40mg/kg is "invariably fatal to humans".

The data show

70	cases of survivors receiving	> 20mg/kg
66		> 40mg/kg
39		> 80mg/kg
22		> 100mg/kg
13		>200mg/kg

These data are of use in defining the upper bands of the dose response curve, but of course are skewed to consider only survivors thus biasing the survival graph.

Marsh notes …" Zeneca quote "An oral dose of about 3g paraquat ion is likely to be fatal, if untreated, to an adult. This equates to approximately 15g of 'Gramoxone' ". A dose of 3g of paraquat equates to approximately **43mg paraquat/kg bodyweight** (for a **70kg** person). Thus the Zeneca statement is not "a million miles" away from the regulator's pronouncement that 20-40mg/kg is invariably fatal."

MgSO4 trial

Japan and Korea/Sri Lanka treatment trial combined

Amount ingested (g)	Number survived	Number dead	Percentage survivors
0-1	14	6	70
1-2	9	7	56
2-3	7	6	54
3-4	6	11	35
>4-15	14	58	24
>15-30	5	40	11
>30	1	29	3

These(limited) data suggest that the median lethal amount ingested is in the region of 1-3g paraquat, or approximately 15-40mg/kg; however, again we do not have bodywts so this has to be treated with caution. To have a 29% (20/69) survival rate from a 3-15g ingestion group is encouraging, and would not have been expected from the statements in the literature that 3g (40mg/kg) is invariably a fatal dose.

I believe this study was terminated after the initial trial as there were considered insufficient patients who had received the amounts of paraquat that were deemed treatable. Additionally, there were indications of effects due to the high magnesium administration.