1970
Baytos report issued (1970)

1975
PST99 at FO molecular level (1975)

1980
CTRU trial started, and decision taken to add PFP79 to FS (1981)

1981
PFP90 tested in cattle with other acute toxic molecules (1981-8)

1993
Mike Ronell left CTL for Phama (1994)

1995
Realisation that systemic control may be suboptimal (1995)

1997
Marion H. Voe and Church & Voe paper (1997)

1998

2000
John Heylings joined to work on safe form (1996)

2001
John Heylings left CTL (1997)

2005
Lewis Smith re-joined CTL (1999)

2010
John Heylings approaches Syngenta (2018)

2015
Closed transfer systems strategy
A new analysis of PP796 human emesis data

Data from Bayliss (1973) summary of clinical data – doses were in mg

<table>
<thead>
<tr>
<th>Drug</th>
<th>Legates</th>
<th>Dose (mg)</th>
<th>No.</th>
<th>Comment/Reason</th>
<th>Bodyweight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ceviz MX</td>
<td>3 trials</td>
<td>10, 20, 40</td>
<td>3</td>
<td>T, V, N</td>
<td>70 kg</td>
</tr>
<tr>
<td>Manchester/Dave et al.</td>
<td>1 trial</td>
<td>10</td>
<td>1</td>
<td>T, V, N</td>
<td>70 kg</td>
</tr>
<tr>
<td>Manchester/Dave et al.</td>
<td>1 trial</td>
<td>20</td>
<td>1</td>
<td>T, V, N</td>
<td>70 kg</td>
</tr>
<tr>
<td>Manchester/Dave et al.</td>
<td>1 trial</td>
<td>40</td>
<td>1</td>
<td>T, V, N</td>
<td>70 kg</td>
</tr>
<tr>
<td>Manley/Kenneth</td>
<td>1 trial</td>
<td>10</td>
<td>1</td>
<td>T, V, N</td>
<td>70 kg</td>
</tr>
<tr>
<td>Pinnock</td>
<td>1 trial</td>
<td>20</td>
<td>1</td>
<td>T, V, N</td>
<td>70 kg</td>
</tr>
<tr>
<td>Pinnock</td>
<td>1 trial</td>
<td>40</td>
<td>1</td>
<td>T, V, N</td>
<td>70 kg</td>
</tr>
<tr>
<td>Pinnock</td>
<td>1 trial</td>
<td>60</td>
<td>1</td>
<td>T, V, N</td>
<td>70 kg</td>
</tr>
</tbody>
</table>

- Exclude Utrecht/Geneve study
- Only used single dose studies for now (using repeat dose only could also be done)
- Convert doses to mg/kg, assuming 70 kg where actual bodyweights unavailable
Angina pectoris

- Manchester/Davies #3 clinical trial in obese subjects
  - Double-blind crossover study
  - 2mg PP796, three times a day, for 6 weeks (or same with placebo)
  - In two subjects, classic angina of effort appeared for the first time ever whilst on PP796, and the trial was abandoned
    - One was 38 yrs, female, 102 kg; the other 33 yrs, female, 83 kg
  - Timing of the angina is unclear, but probably reported at 4 and 6 weeks for these subjects, respectively
  - The appearance of angina pectoris in 2 subjects in whom the cardiovascular system was clinically normal was apparently due to the compound
  - Since withdrawal no more attacks were recorded, even on severe exercise

- Current company PP796 Occupational Exposure Standard was set in 1989 (and reported in 1994 as OES0002C)
  - Critical acute effect taken to be nausea and vomiting, on which the standard was set; in order to protect against angina pectoris, which was taken to be the critical chronic effect
A new analysis of PP796 human emesis data

<table>
<thead>
<tr>
<th>Dose (mg)</th>
<th>Body weight</th>
<th>Dose (mg/kg)</th>
<th>n</th>
<th>n (combined)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.25</td>
<td>(mg)</td>
<td>0.0164</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>0.5</td>
<td>(mg)</td>
<td>0.0328</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>(mg)</td>
<td>0.0657</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>(mg)</td>
<td>0.1314</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>(mg)</td>
<td>0.2629</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>(mg)</td>
<td>0.5257</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>16</td>
<td>(mg)</td>
<td>1.0513</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

- Fit a dose-response
  - Using Probit function for probability of vomiting (assumes vomiting threshold is normally distributed on a log-dose scale, where dose is expressed in mg/kg)
  - Assuming binomially distributed errors, taking differing group sizes into account
A new analysis of PP796 human emesis data

Curve fits the data well:
- Best estimate of the dose giving 50% probability of vomiting is 0.05 mg/kg, i.e. 3.5mg
- Best estimate of the dose giving 90% probability of vomiting is 0.11 mg/kg, i.e. 7.7mg
A new analysis of PP796 human emesis data

Curve fits the data well
- Best estimate of the dose giving 50% probability of vomiting is 0.05 mg/kg, i.e. 3.5 mg
- Best estimate of the dose giving 90% probability of vomiting is 0.11 mg/kg, i.e. 7.7 mg

But this ignores the massive uncertainty
- Confidence limits for the dose giving 50% probability are 0.03-1.4 mg/kg, i.e. 2.1-101 mg
- Confidence limits for the dose giving 90% probability are 0.00-156 mg/kg, i.e. 0.2-10920 mg
Comparing human and NHP dose-responses

- Best estimate of the dose giving 50% probability of vomiting is 0.52 mg/kg, 10x higher than for the human data.
Comparing human and NHP dose-responses

Curve fits the data well
- Best estimate of the dose giving 50% probability of vomiting is 0.52 mg/kg, 10x higher than for the human data.
Comparing human and NHP dose-responses

Fitting a common slope to both datasets

There is no statistical justification for using separate slopes for the human and NHP datasets. The differences between the curves and the data is consistent with chance.
Comparing human and NHP dose-responses

Fitting single dose-response to both datasets

There is no statistical justification for fitting different dose-responses to the human and nhp datasets.
The differences between the curve and the data is consistent with chance.
Best estimate of the dose giving 50% probability of vomiting is 0.55 mg/kg with confidence limits 0.29-2.5 mg/kg; for a 70kg human this is 38 mg (20-175 mg/kg).
Comparison of the new analysis with that in CTL/R/390

The choice of human data to use for the two analyses differs somewhat, but this doesn't much affect the outcome.

Best estimates of the human and rhp dose-responses leads you to suppose that humans are 10x more sensitive than rhps, which agrees with CTL/R/390.

- However, this does not take uncertainty into account. The data do not precisely define the dose-responses.
- In fact, there is no statistical evidence for a difference in dose-response between humans and rhps.
- The data have been over-interpreted in CTL/R/390.
  - Uncertainty was not taken into account.
  - The steepness of the human dose-response was over-estimated.
  - The apparent species difference is not robust.
  - The conclusion that 5 mg emetic in 10 ml of formulation "should be sufficient to ensure that most people ingesting 10ml will vomit" is not supported by a robust analysis of the data.
  - However, not taking statistical uncertainty into account is very common in the scientific community, and anyone not doing so could come to the same conclusions as those in CTL/R/390.
Questions
- What does a robust interpretation of the emesis data show, and in this light, what do we think about CTLUR/390?
- What were the new developments and decisions about emetic inclusion level in this period, and why were these decisions taken?
- How did the Inlexon project go from being so promising to closing?
- What can be done now to reduce paracuel poisonings?
## ICI PQ studies in cynomolgus macaques in 1970s

<table>
<thead>
<tr>
<th>Subject</th>
<th>Drug</th>
<th>Treatment</th>
<th>Duration</th>
<th>Route</th>
<th>Alscy</th>
<th>Max Blood Level</th>
<th>Results with DMSO</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>Carageen</td>
<td>LOW</td>
<td>Methylpred</td>
<td>7 days</td>
<td>I.V.</td>
<td>100 ng/mL</td>
<td>No symptoms</td>
<td>Report, by Dr. Ricks, Ph.D. from ICI, 1971</td>
</tr>
<tr>
<td>Female</td>
<td>Carageen</td>
<td>LOW</td>
<td>Prednisolone</td>
<td>7 days</td>
<td>I.V.</td>
<td>100 ng/mL</td>
<td>No symptoms</td>
<td>Report, by Dr. Ricks, Ph.D. from ICI, 1971</td>
</tr>
<tr>
<td>Female</td>
<td>Carageen</td>
<td>LOW</td>
<td>Prednisolone</td>
<td>7 days</td>
<td>I.V.</td>
<td>100 ng/mL</td>
<td>No symptoms</td>
<td>Report, by Dr. Ricks, Ph.D. from ICI, 1971</td>
</tr>
</tbody>
</table>

*Report on animal studies conducted at ICI, London in 1970s.*
ICI PQ studies in cynomolgus macaques in 1970s

<table>
<thead>
<tr>
<th>Date</th>
<th>Dose (mg/kg)</th>
<th>Route</th>
<th>Duration (days)</th>
<th>PQ induction</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1970</td>
<td>10</td>
<td>i.p.</td>
<td>7</td>
<td>100 mg</td>
<td>Vomiting</td>
</tr>
<tr>
<td>1971</td>
<td>5</td>
<td>i.v.</td>
<td>30</td>
<td>50 mg</td>
<td>No effect</td>
</tr>
<tr>
<td>1972</td>
<td>2</td>
<td>s.c.</td>
<td>15</td>
<td>25 mg</td>
<td>Vomiting</td>
</tr>
</tbody>
</table>

- Design of PQ study was very different to the others, making comparisons difficult
- PP796 doses very high, and very effective at inducing early vomiting
- Despite this the magnitude of benefit of PP796 was modest
- No clear relationship of benefit of PP796 to AI irritancy
Emetic
Questions

What does a robust interpretation of the emesis data show, and in this light what do we think about CTL/R/390?

What were the new developments and decisions about emetic inclusion level in this period, and why were these decisions taken?

How and why did the Inteon project go from being so promising to closing?

What can be done now to reduce paraquat poisonings?

1970
PP796 +/- PQ tested in NHPs (1975)
CTL/R/390 interpretation of clinical data issued
Decision taken to add PP796 to PQ

1975

1980

1985
Realisation that emetic conc may be suboptimal (mid '80s)

1990
Emetic review (1991)

1995
Magnoxone project

2000
Inteon project

2005
Inteon review with externals @CTL (2006)

2010
Global Inteon slideset (2008)

2015

2019
Current situation
1970
Bayliss report issued (1973)

1975
PP796 +/- PQ tested in NHPs (1975)
CTL/R/390 issued, and decision taken to add PP796 to PQ (10/1976)
PP796 tested in NHPs with other acutely toxic molecules (1977-9)

1980

1985
Realisation that emetic conc may be suboptimal (1985)
Meredith & Vale and Onyon & Volans papers (1987)
Jon Heylings joined to work on safer formn (1986)

1990
Jon wrote to Lewis re emetic (1/1990); TRC review (1990)
Emetic review commissioned (1991)

1995
Magnoxone project

1995
Inteon project

2000
Sri Lanka 1 (2003-6)

2005
Inteon review with externals @CTL (2006)
Global Inteon slideset (2008)

2010
Closed transfer systems strategy

2015

2019
Jon Heylings approaches Syngenta (2018)

Lewis Smith joined CTL (1972)
Mike Rose left CTL for Pharms (1984)
Jon moved Sections (1991); Lewis left CTL (4/1991)
Lewis Smith re-joined CTL (1999)
Jon Heylings left CTL (2007?)
A new analysis of PP796 human emesis data

Data from Bayliss (1973) summary of clinical data – doses were in mg

<table>
<thead>
<tr>
<th>Trial</th>
<th>Subjects</th>
<th>Doses</th>
<th>n</th>
<th>n vomitted (time)</th>
<th>Body weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dundee/Crooks</td>
<td>Fit students</td>
<td>1 x 0.25 to 8 mg</td>
<td>12</td>
<td>2 (30' &amp; 120')</td>
<td>69 kg</td>
</tr>
<tr>
<td>Manchester/Davies #1</td>
<td>Fit students</td>
<td>1 x 2mg</td>
<td>8</td>
<td>1 (45')</td>
<td>no data</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 x 2mg with 7 day</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Manchester/Davies #2</td>
<td>Fit volunteers</td>
<td>interval</td>
<td>2</td>
<td>0</td>
<td>no data</td>
</tr>
<tr>
<td>Glasgow/Kerr</td>
<td>Allergic asthmatic 18-45</td>
<td></td>
<td>4</td>
<td>1 (no time stated)</td>
<td>no data</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 x 2mg with</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aberdeen/Palmer</td>
<td>Asthmatic 18-45</td>
<td>unspecified interval</td>
<td>1</td>
<td>0</td>
<td>71 kg</td>
</tr>
<tr>
<td>Aberdeen/Palmer</td>
<td>Asthmatic 18-46</td>
<td>1 x 2mg</td>
<td>1</td>
<td>1 (20')</td>
<td>70 kg</td>
</tr>
<tr>
<td></td>
<td>Mild to moderate</td>
<td>single unspecified dose</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Utrecht/Beumer</td>
<td>emphysema</td>
<td></td>
<td>12</td>
<td>not recorded</td>
<td>no data</td>
</tr>
<tr>
<td></td>
<td>Classic endogenous</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Edinburgh/Eccleston</td>
<td>depression 18-60</td>
<td>21 days, 3 x 2 mg</td>
<td>4</td>
<td>0</td>
<td>no data</td>
</tr>
<tr>
<td></td>
<td>Chronic inpatient</td>
<td>7 days, 3 x 1 mg, then</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Birmingham/Magnus #1</td>
<td>schizophrenia</td>
<td>7 days, 3 x 2 mg</td>
<td>6</td>
<td>0</td>
<td>134 kg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7 days, 3 x 1 mg, then</td>
<td></td>
<td>1 (no time, but</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>whilst on 2mg</td>
<td></td>
<td>whilst on 2mg</td>
<td>126 kg</td>
</tr>
<tr>
<td>Birmingham/Magnus #2</td>
<td>Anxiety 18-50</td>
<td>7 days, 3 x 2 mg</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sustained diastolic</td>
<td>7 days, 3 x 2 mg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bebington/Zacharias</td>
<td>hypertension 18-60</td>
<td>28 days, 4 x 2 mg</td>
<td>3</td>
<td>0</td>
<td>77 kg</td>
</tr>
<tr>
<td>Manchester/Davies #3</td>
<td>Obesity 30-55</td>
<td>42 days, 3 x 2 mg</td>
<td>4</td>
<td>0</td>
<td>123 kg</td>
</tr>
</tbody>
</table>

- Exclude Utrecht/Beumer study
- Only used single dose studies for now (using repeat dose only could also be done)
- Convert doses to mg/kg, assuming 70kg where actual bodyweights unavailable
Angina pectoris

- Manchester/Davies #3 clinical trial in obese subjects
  - Double-blind crossover study
  - 2mg PP796, three times a day, for 6 weeks (or same with placebo)
  - In two subjects, classic angina of effort appeared for the first time ever whilst on PP796, and the trial was abandoned
    - One was 38 yrs, female, 102 kg; the other 33 yrs, female, 83 kg
  - Timing of the angina is unclear, but probably reported at 4 and 6 weeks for these subjects, respectively
  - The appearance of angina pectoris in 2 subjects in whom the cardiovascular system was clinically normal was apparently due to the compound
  - Since withdrawal no more attacks were recorded, even on severe exercise

- Current company PP796 Occupational Exposure Standard was set in 1989 (and reported in 1994 as OES0002C)
  - Critical acute effect taken to be nausea and vomiting, on which the standard was set, in order to protect against angina pectoris, which was taken to be the critical chronic effect
A new analysis of PP796 human emesis data

<table>
<thead>
<tr>
<th>Dose (mg)</th>
<th>Body weight</th>
<th>Dose (mg/kg)</th>
<th>n</th>
<th>n (vomitted)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.25</td>
<td>70</td>
<td>0.0036</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>0.5</td>
<td>70</td>
<td>0.0071</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>130</td>
<td>0.0077</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>70</td>
<td>0.014</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>123</td>
<td>0.016</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>70</td>
<td>0.029</td>
<td>19</td>
<td>3</td>
</tr>
<tr>
<td>3</td>
<td>70</td>
<td>0.043</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>70</td>
<td>0.057</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>8</td>
<td>70</td>
<td>0.11</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

- **Fit a dose-response**
  - Using Probit function for probability of vomiting (assumes vomiting threshold is Normally distributed on a log-dose scale, where dose is expressed in mg/kg)
  - Assuming binomially distributed errors, taking differing group sizes into account
A new analysis of PP796 human emesis data

Curve fits the data well
- Best estimate of the dose giving 50% probability of vomiting is 0.05 mg/kg, ie 3.5mg
- Best estimate of the dose giving 90% probability of vomiting is 0.11 mg/kg, ie 7.7mg
A new analysis of PP796 human emesis data

Curve fits the data well
- Best estimate of the dose giving 50% probability of vomiting is 0.05 mg/kg, ie 3.5mg
- Best estimate of the dose giving 90% probability of vomiting is 0.11 mg/kg, ie 7.7mg

But this ignores the massive uncertainty
- Confidence limits for the dose giving 50% probability are 0.03-1.4 mg/kg ie 2.1-101 mg
- Confidence limits for the dose giving 90% probability are 0.06-156 mg/kg ie 4.2-10920 mg
Comparing human and NHP dose-responses

nhp (n=85)

Curve fits the data well

- Best estimate of the dose giving 50% probability of vomiting is 0.52 mg/kg, 10x higher than for the human data.
Comparing human and NHP dose-responses

Curve fits the data well
- Best estimate of the dose giving 50% probability of vomiting is 0.52 mg/kg, 10x higher than for the human data.
Comparing human and NHP dose-responses

Fitting a common slope to both datasets

There is no statistical justification for using separate slopes for the human and nhp datasets.

The differences between the curves and the data is consistent with chance.
Comparing human and NHP dose-responses

Fitting single dose-response to both datasets

There is no statistical justification for fitting different dose-responses to the human and nhp datasets.

The differences between the curve and the data is consistent with chance. Best estimate of the dose giving 50% probability of vomiting is 0.55 mg/kg with confidence limits 0.29-2.5 mg/kg: for a 70kg human this is 38 mg (20-175 mg/kg)
Comparison of the new analysis with that in CTL/R/390

The choice of human data to use for the two analyses differs somewhat, but this doesn’t much affect the outcome.

Best estimates of the human and nhp dose-responses leads you to suppose that humans are 10x more sensitive than nhps, which agrees with CTL/R/390:

- However, this does not take uncertainty into account. The data do not precisely define the dose-responses.
- In fact, there is no statistical evidence for a difference in dose-response between humans and nhps.

● The data have been over-interpreted in CTL/R/390:
  - Uncertainty was not taken into account
  - The steepness of the human dose-response was over-estimated
  - The apparent species difference is not robust
  - The conclusion that 5 mg emetic in 10 ml of formulation “should be sufficient to ensure that most people ingesting 10ml will vomit” is not supported by a robust analysis of the data.
  - However, not taking statistical uncertainty into account is very common in the scientific community, and anyone not doing so could come to the same conclusions as those in CTL/R/390.
Questions

What does a robust interpretation of the emesis data show, and in this light what do we think about CTL/R/390?

What were the new developments and decisions about emetic inclusion level in this period, and why were these decisions taken?

How and why did the Inteon project go from being so promising to closing?

What can be done now to reduce paraquat poisonings?
## ICI PQ studies in cynomolgus macaques in 1970s

<table>
<thead>
<tr>
<th>Study</th>
<th>Date</th>
<th>Test material</th>
<th>Volume dosed</th>
<th>Doses</th>
<th>N/group</th>
<th>Results without PP796</th>
<th>Results with PP796</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paraquat alone</td>
<td>Conducted 1974</td>
<td>PQCl2 + water</td>
<td>40 ml</td>
<td>IV 6, 10, 16, 24, 32 &amp; 40 mg PQion/kg; Oral 45, 55, 65, 85 mg PQion/kg</td>
<td>1 to 6</td>
<td>IV survived at 6 mg/kg but died at higher doses; Oral 1/6, 0/2, 3/6 &amp; 5/6 died at each dose</td>
<td>Both survived at 100 &amp; 250 mg/kg but died at 500 mg/kg</td>
<td>HLS 1975 study report, Purser &amp; Rose 1979 paper</td>
</tr>
<tr>
<td>Paraquat + PP796</td>
<td>Reported 1976</td>
<td>Gramoxone + &quot;an emetic dose of PP796&quot; + water Gramoxone 20% formulation + 10g Complan +/- PP796 + water</td>
<td>Formulation volume + 100ml water</td>
<td>Oral 100, 250 &amp; 500 mg PQion/kg + unknown PP796 dose</td>
<td>2</td>
<td></td>
<td>6/8 vomited within 1 hour and survived, 2/8 vomited at 4-8 hours and died</td>
<td>CTL/R/391 1976 summary</td>
</tr>
<tr>
<td>Paraquat +/- PP796</td>
<td>Reported 1976</td>
<td></td>
<td>20 ml</td>
<td>Oral 100 mg PQion/kg +/- 2 mg PP796/kg</td>
<td>8</td>
<td>7/8 vomited 3-6 hours, and all died within 2 days</td>
<td></td>
<td>CTL/R/391 1976 summary</td>
</tr>
</tbody>
</table>

Classification: INTERNAL USE ONLY
### ICI PQ studies in cynomolgus macaques in 1970s

<table>
<thead>
<tr>
<th>Study</th>
<th>Irritancy of AI</th>
<th>Date</th>
<th>Test material</th>
<th>Volume</th>
<th>N/group</th>
<th>Doses without PP796</th>
<th>Results without PP796</th>
<th>Doses with PP796</th>
<th>Results with PP796</th>
<th>Report conclusion</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paraquat +/- PP796</td>
<td>Irritant</td>
<td>Reported 1976</td>
<td>Gramoxone 20% formulation + 10g Complan +/- PP796 + water</td>
<td>20 ml</td>
<td>8</td>
<td>100 mg PQion/kg</td>
<td>7/8 vomited 3-6 hours, and all died within 2 days</td>
<td>100 mg PQion/kg + 2 mg PP796/kg</td>
<td>6/8 vomited within 1 hour and survived, 2/8 vomited at 4-8 hours and died</td>
<td>(Clear benefit)</td>
<td>CTL/R/391 1976 summary</td>
</tr>
<tr>
<td>Diquat +/- PP796</td>
<td>Irritant</td>
<td>Conducted 1977</td>
<td>DOBr2 +/- PP796 + water</td>
<td>50 ml</td>
<td>2 or 4</td>
<td>100, 200, 300 &amp; 400 mg PQion/kg</td>
<td>All vomitted at 47-180 mins, 1/2, 0/4, 1/2 &amp; 2/2 died</td>
<td>400-4, 800-8, 800-16, 1200-24 &amp; 1600-32 (mgPQion/kg+mPP796/kg)</td>
<td>All vomitted 3-18 mins, 0/2, 1/4, 1/2 &amp; 2/2 died</td>
<td>Animals dosed PP796 generally survived higher doses of DQ. LD50 was 200-400 without and 800-1600 with PP796.</td>
<td>CTL/C/576</td>
</tr>
<tr>
<td>Parathion +/- PP796</td>
<td>Not irritating</td>
<td>Conducted 1977</td>
<td>Parathion +/- PP796 + water</td>
<td>100 ml</td>
<td>2 or 4</td>
<td>8, 75, 100, 150 &amp; 200 mg/kg</td>
<td>6/8 vomitted at top three doses at 50-100 mins, 0/2, 1/2, 2/4, 2/2 &amp; 2/2 died.</td>
<td>200+2, 400+4, 500+5 (mgPion/kg+mPP796/kg)</td>
<td>All vomitted at 5-16 mins and 0/2, 2/4 &amp; 1/2 died</td>
<td>At least 4x benefit</td>
<td>CTL/C/746</td>
</tr>
<tr>
<td>Malathion +/- PP796</td>
<td></td>
<td>Reported 1977</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CTL/C/748 (not found)</td>
</tr>
<tr>
<td>Ethylene glycol +/- PP796</td>
<td>Mildly irritating</td>
<td>Conducted 1979</td>
<td>Ethylene glycol +/- PP796 + water</td>
<td>20 ml/kg (50-88 ml)</td>
<td>2</td>
<td>1000, 2000 &amp; 4000 mg/kg</td>
<td>Vomitted only at top two doses, at 2-22 hours, and 0/2, 0/2 &amp; 2/2 died</td>
<td>4000-2, 16000-8 (mgEGion/kg+mPP796/kg)</td>
<td>All vomitted at 2-15 mins, 0/2 &amp; 1/2 died</td>
<td>Around 4x benefit</td>
<td>CTL/C/728</td>
</tr>
<tr>
<td>Carbofuran +/- PP796</td>
<td>Mildly irritating</td>
<td>Conducted 1979</td>
<td>Carbofuran +/- PP796 + water</td>
<td>20 ml/kg (46-86 ml)</td>
<td>2</td>
<td>5, 10, 20 &amp; 40 mg/kg</td>
<td>None vomitted, only top dose group died</td>
<td>40+2, 40+4 (mgCion/kg+mPP796/kg)</td>
<td>40+2 did not vomit and died, 40+4 vomitted at 3-4mins and 1/2 died</td>
<td>No clear indication of benefit</td>
<td>CTL/C/775</td>
</tr>
</tbody>
</table>

- Design of PQ study was very different to the others, making comparisons difficult
- PP796 doses very high, and very effective at inducing early vomiting
- Despite this the magnitude of benefit of PP796 was modest
- No clear relationship of benefit of PP796 to AI irritancy