Message

From: Hall Mike M [/O=ZENECA/OU=ALDERLEY/CN=RECIPIENTS/CN=MIKE.HALL]
Sent: 7/15/1998 8:18:37 AM
To: Heylings Jon JR [/O=ZENECA/OU=ALDERLEY/cn=Recipients/cn=Jon.Heylings]
CC: Lock Ted EA [/O=ZENECA/OU=ALDERLEY/cn=Recipients/cn=Ted.Lock]; Clapp Mike MJL [/O=ZENECA/OU=ALDERLEY/cn=Recipients/cn=Mike.Clapp]; Ishmael John J [/O=ZENECA/OU=ALDERLEY/cn=Recipients/cn=John.Ishmael]; Allen Sandra SL [/O=ZENECA/OU=ALDERLEY/cn=Recipients/cn=Sandra.Allen]; Berry Dave DJ [/O=ZENECA/OU=ALDERLEY/cn=Recipients/cn=Dave.Berry]
Subject: Pg absorption

Importance: High

Jon,

I think the last statement in your reply says it all - "assuming the conditions of the study are appropriate". I don't doubt that by using different formulations and different routes of administration it is possible to get good absorption of pq but what matters is the absorption under the conditions used in the study which produced the NOEL.

If you were to repeat the dog tox study using a liquid formulation administered by gavage which resulted in a higher absorption then you would expect a correspondingly lower NOEL (unless you are suggesting that toxicity is not linked to systemic exposure). The fact that the extraction procedures used during diet analysis only resulted in ~ 40% recovery suggests that pq binds to diet and may not be available for absorption.

I am sure that any data suggesting a higher absorption figure would be attractive to the business but unless there is a corresponding assessment of toxicity under the same conditions it would be difficult to justify it's use. The fact that a low absortion was estimated and reported in the pivotal dog tox study is going to be difficult to overcome.

Mike

From: Heylings Jon JR
Sent: 14 July 1998 16:38
To: Lock Ted EA; Clapp Mike MJL; Ishmael John J; Allen Sandra SL; Berry Dave DJ; Hall Mike M
Subject: RE: Bipyridyl RIM

Dave et al,

My perspective on dog oral absorption of PQ is as follows:

My group have conducted over 30 dog studies (1986-1994) on paraquat formulations by capsule and gavage dosing. IRI also did work for Bob Scott in 1987 (which was never reported) on Gramoxone W, Gramoxone S and Preeglox. Together, all this work indicated that absorption was higher in dogs than the rat and probably in the region of (20-30%). The surfactant-containing products are generally more bioavailable, due to their effects on mucosal damage - as also occurs in the rat.

A more definitive dog study on paraquat absorption, distribution and elimination was carried out by my group as part of our understanding of the role of the emetic in an SDS gel formulation of paraquat (XD1275). Here, we conducted a mass balance study in the dog - reported by Lewis Smith and myself as a file report. (This, I believe was never issued as a CTL report but was reported directly to the Business and ICI Japan). However, I have located my copy in my files and even have slides on this work.

In this study we ran a Gramoxone low dose control at 8mg/kg gavage, i.e. below the MLD. The balance study found **32.9% of the oral dose in the urine 0-48h**, plus a trace more in tissues post mortem.

This is sound data clearly demonstrating that about one third of the dose is absorbed. Data are reproducible for 3 animals and the radiochemical recovery etc. was performed by M&P (Harold Bratt). Incidently, about 55% of the dose was found in the faeces. If this research work helps our cause we could cut the relevant part of this out of the "report" and use it to advance the case for higher absorption in the dog, assuming the conditions of the study are appropriate.

Jon R Heylings

Tel: 01625 514530 Fax: 01625 586396
E-Mail: Jon.Heylings@CTI.Zeneca.COM

From: Hall Mike M
Sent: 14 July 1998 11:51
To: Lock Ted EA; Heylings Jon JR; Clapp Mike MJL; Ishmael John J; Allen Sandra SL; Berry Dave DJ
Subject: RE: Bipyridyl RIM
Importance: High

Dave,

The issue of absorption of paraquat from diet by dogs has been checked previously (see attached), as the measurements were made during the tox study and the results were included in the report they are difficult to ignore. I don't have an electronic copy of the original query from Andy Cook (it was all-in -one days) but I do have a paper copy. If you need to discuss please contact me.

Mike
<<Message: Paraquat absorption>>

From: Berry Dave DJ
Sent: 07 July 1998 17:07
To: Lock Ted EA; Heylings Jon JR; Clapp Mike MJL; Ishmael John J; Hall Mike M; Allen Sandra SL
Subject: Bipyridyl RIM
Importance: High

The bipyridyl RIM is now scheduled for Thursday 23 July, 2-5pm. Jon is on leave and ted may be away on business - thus I would appreciate a good brief on current activities to feed into the RIM.

The last RIM was on 27 Nov 97; the actions against CTI folk were as follows - please let me know what progress has been made, what is outstanding and the impact of any results;

Note - the following is my understanding of the issues - please correct is wrong;

1. Pq and Dq AOELs in EU

EU currently bases AOEL on a default oral absorption factor of 10% for Dq and Pq. DG VI uses actual absorption factor where there is evidence absorption is <15%.
In the rat metab studies, dq absorption is 3-6%: pq 10%. However, for pq the dog is used for the tox endpoint in worker risk assessments, therefore if we can demonstrate higher oral absorption factor, this will be taken into consideration. Ted and Jon believe the true value is higher than 10%, possibly as high as 30-40% for Gramoxone S and Gramoxone W formulations.

DJB to gather info for consideration by NSH PT.

2. Dermal Bioavailability

The RIM agreed
- that the in vitro interspecies data base using specific activity material be increased
- low volume in vitro data be developed to compliment human volunteer studies
- in vivo (rodent and rabbit) studies be supported by obtaining iv dose recovery data using primates (Action was on Bob - was this done?)

Has any of this work been started?

3. Diquat Cataracts

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- there was support for studies to show **strain** differences in the development of cataract - RCS was to bring back proposals to a liaison meeting looking at dose/time/repeat pulse of dose and relevance to field exposure. Was this done?- still waiting for TWERF from Fernhurst (SJS) for 90 day oral study
- update on Dr Spector's proposal (Ted)
- at a HELP meeting there was a recommendation to consider conducting a dermal 90 day cataract study with dq - I will get further info.

Enlightenment on why it was decided not to investigate recovery from the lesion would be appreciated.

4. Potential for uptake of pq in lung - differences between man and dog.

Action was for Ted to give a definitive assessment of relative rates (man and dog) - pb/pk modelling to extrapolate across species. Has this been accomplished?

5. Neurotoxicity

What is the lab's current position on the ability of pq (and dq) to cross the BBB - and what is the impact of this on the potential for BiPs to be associated with Parkinsonism?
Presumably the liaison with California institute is still ongoing - what is the current progress of their research? Are they also working with dq?
Are we keeping abreast of Eriksson's work? - action was on Ted and Mike as there were wider implications than just for pq (eg pyrethroids); action and consideration of regulatory impact was due to be completed by end March 98..

6. Skin Irritation

Agreed to the proposal to assess if pq entered through hair follicles.This is ongoing - Jon, can you please give me an update on progress? Thanks. (I assume the programme is as outlined in Jon and Linda Bishop's proposal "BiP Skin Irritation Research Proposal" - undated?)

7. Analysis of pq poisoning cases

Was Ian Pate's analysis issued? - was being reviewed by the business with the aim to issue Jan 98..

Prepare a case for rebutting R25 classification - completed by MJLC.

8. MgSO4 project

Jon, please let me have an update; the minute actually states that it is strongly supported that CTL resources be focussed on providing analytical and clinical support rather than additional mechanistic understanding ... is this the case?

9. Inhalation

This is the other area where I know we will have to put effort; Colin Coutts is currently summarising the available data. The objective from the business is for us to consider how we might get away from Cat I toxicity classification (not a problem in the USA, but repercussion in Japan and ROW.
- in the inhalation hazard predictive for man?(quantitative/qualitative?)
- is the rat the most appropriate species ? - probably yes
- comparison of ai v formulation... spray strength?

What other activities are ongoing - or proposed?

Feedback asap appreciated - failing which we have an NSH PT meeting scheduled for Tuesday 14 July.

Thanks,