
From: Sheldon Ros GBAP
Sent: Tuesday, October 01, 2002 1:44 PM
To: Wheals Ian CHBS
Cc: Clapp Mike GBAP
Subject: RE: Tox data potentially for FAO spec submission in October

Ian,

I spent some time last week trying to identify what data we have on the substances listed. The bottom line is that the database is very poor for most of the impurities listed - the data (where available) are old, in many cases we don't have the original reports (if indeed there were any, much of what I found was cited in old correspondence) and much of the quality (vs current standards) is poor and wouldn't stand close scrutiny.

The exceptions are for PP796 and cyanide.

The original database on PP796 is old - the original safety evaluation was done at Pharms but, despite seeing some summaries of the toxicology data, I want to track down all the original reports and pull together a decent overview. In doing some digging through records at CTL and Fernhurst (and for that matter Pharms), I actually found a carcinogenicity study that I didn't know existed so I think it will be a worthwhile exercise, although it will take me a while to complete given other work pressures at the moment. The summary will concentrate on the toxicology of PP796, not it's efficacy as an emetic (which was summarised in MII Section 3 Appendix A).

There is a wealth of data on cyanide. A fairly recent review (Toxicology profile for cyanide, draft, Feb 20th 1996, 615.9 UN Ref) published by the Department of Health and Human Services in the USA is available. There is also a Syngenta toxicology position statement, written by Jeorg Herbst, on HCN in trinexapac-ethyl: derivation of a level of no concern. I have asked him to send me the final version of this document since my version is a draft dated Jan 2002. With modification, this could perhaps be used to support a case for a limit on no concern for PQ formulations.

Apart from that I don't believe the toxicology data could be used to justify limits in manufactured products.

Mike is away this week but upon his return we probably need to agree where we go from here.

On a non-work front, many congratulations on the birth of your little one, I remember this stage well - you're probably shattered!!

Best wishes

Ros

Ros Sheldon

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-----Original Message-----

From: Wheals Ian CHBS
Sent: 27 August 2002 16:39
To: Clapp Mike GBAP
Subject: Tox data potentially for FAO spec submission in October

Mike,

An evaluation of various generic paraquats did not help identify many specific impurities that could be considered toxicologically or ecotoxicologically significant. Consequently the revised FAO specification submission will likely name

- 4,4-bipyridyl. The maximum limit to be proposed by Syngenta will likely be 0.2% (as in the existing specification)
- Terpyridines. The maximum limit to be proposed by Syngenta for total terpyridine content (or total terpyridyl content) will likely be 0.5ppm.

If we can justify a case for toxicological or ecotoxicological significance, the revised FAO specification submission may also name

- 1-methyl Pyridinium (MPC). The maximum limit to be proposed by Syngenta will likely be 0.2ppm
- 1'-methyl-2,4'-bipyridinium. The maximum limit to be proposed by Syngenta will likely be 0.25ppm

Whilst they will not make the FAO spec more challenging for generics we may wish to look at what we know of the toxicology of some other impurities as this may have a bearing on the credibility of our case for the impurities we do want to classify as toxicologically significant.

- 1-methyl-4,4'-bipyridinium ion
- 1-methyl-4-(N-methyl-2-pyridone-4-yl)pyridinium ion

For credibility we may have to include cyanide in the FAO specification. Not sure how we will want to report this if we do go down this route, free cyanide ? or total cyanide or some other description.

Regarding the emetic, in the revised FAO specification submission we will likely seek to add the comment to the effective emetic requirement that

- PP796, 2-amino-4,5-dihydro-6-methyl-4-propyl-s-triazole-[1,5-a]pyrimidin-5-one is the only emetic known to meet these effective emetic criteria
- If PP796 is the effective emetic employed, it must be present at a minimum level of X. (X will likely be equivalent to 0.5ppm in a 20% ion paraquat formulation, but expressed as a ratio to paraquat ion content)

For now please try to identify any data for

- Terpyridines
- 4,4-bipyridyl (R008331)
- 1-methyl pyridinium ion (MPC) (R011815)
- 1'-methyl-2,4'-bipyridinium ion (R011698)
- 1-methyl-4,4'-bipyridinium ion (R009170)
- 1-methyl-4-(N-methyl-2-pyridone-4-yl)pyridinium ion (R030499)
- cyanide
- PP796

Thanks,

Ian