Position Document on Surfactants and INTEON Technology

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During the last few years, a number of Paraquat and Paraquat/Diquat formulations containing the INTEON technology components: alginate, emetic and purgative, have been tested in our in vivo toxicokinetic models. The original INTEON concept was optimised for a 200g/l Paraquat only formulation. This contained built-in wetters and most closely represented the major product Gramoxone. The lead formulation in terms of bioefficacy and safening in our rabbit and dog animal models was A3879BU.

As the research project developed in the period 2001-2003 the INTEON technology was incorporated into the so-called "Daughter" formulations as part of the regulatory strategy to replace all the various bipyridyl products around the world with those containing the INTEON technology. This included higher and lower paraquat strength products and mixtures of paraquat and diquat e.g. the Sprayseed replacement for Australia.

About the same time we had observed stability issues with the lead 200g/l built-in wetter INTEON candidate, A3879BU. A variety of manufactured batches both fresh and stored as well as poured-off samples were tested in the rabbit and dog. Essentially, the safening of these variants of A3879BU never exceeded the 128mg/kg paraquat ion level and in some cases deterioration in toxicological performance occurred. Only the fully homogenous material achieved the required safening level (CTL/XD7201).

A generally better toxicological performance emerged with the two surfactant-free daughter INTEON formulations. By their very nature these are preparations that cannot separate into oil and water phases. They have no hydrophilic/lipophilic surfactants. All the ingredients including the active, alginate, emetic, purgative and dye/stench alerts are water soluble.

The two formulations, a US INTEON, A7831K, containing 240g/L paraquat and an Australian INTEON, A12984D, containing paraquat (135g/L) and diquat (115g/L) were well tolerated up to and including 128mg/kg paraquat ion. In fact, the toxic dose of these formulations was not established in the dog since the objective was to reach this target 128mg/kg paraquat dose with minimal signs of toxicity. The evidence that these two surfactant-free formulations may be less toxic than homogenous A3879BU is supported by the relative plasma values at the two highest doses, 64 and 128mg/kg paraquat ion in the dog. The mean values are shown in Figure 1. The individual animal data shows this best. As shown in Figure 2, the individual AUC values are generally lower for the two surfactant-free INTEONs.

Figure 1

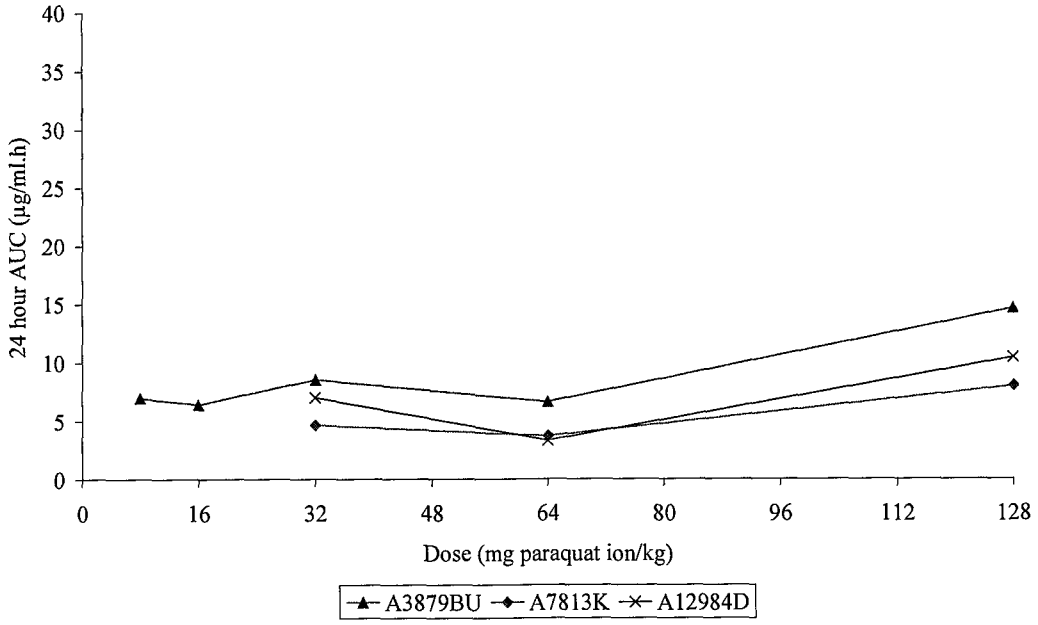
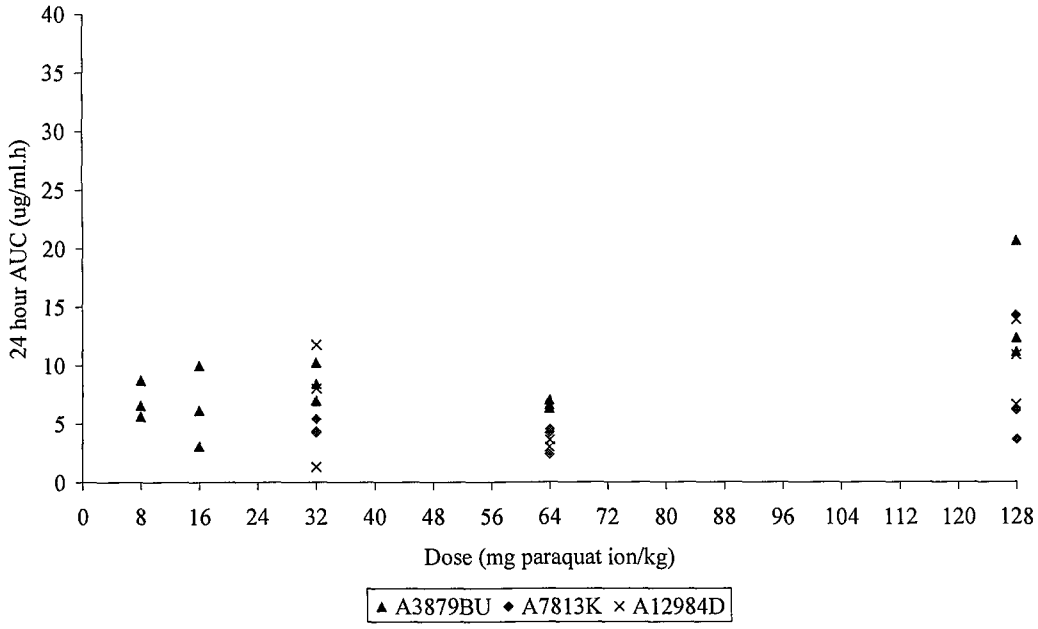


Figure 2



Further evidence that surfactant-free INTEON formulations may be less toxic than their counterpart surfactant-containing systems comes from the rabbit kinetics with the same formulations described above. As shown in Table 1, the homogenous A3879BU formulation gave higher AUC values at 0-1, 0-4 and 0-24h than the surfactant-free INTEONs, A12984B (Australia type with pyridine stench; CTL XB7427) and A7813K (US type; CTL/XB7326). In this non-vomiting species, the early 0-1h AUC is probably the most important with regard to safening performance. However, across the full time exposure the non-surfactant INTEONs look more promising by virtue of the fact that the plasma paraquat levels are lower than the surfactant-containing A3879BU formulation.

Table 1 Rabbit systemic paraquat exposure for 3 INTEON formulations dosed orally at 40mg/kg

		Paraquat AUC (μg/ml.h)		
	Surfactants	1h	4h	24h
A3879BU	Yes	8.88 ± 1.7	21.5 ± 3.9	47.4 ± 9.0
A12984B	No	0.63 ± 0.1	4.20 ± 0.6	17.0 ± 2.3
A7813K	No	0.64 ± 0.2	6.52 ± 1.0	16.8 ± 2.5

Further work is required to substantiate this observation that INTEON technology may be more effective in the absence of surfactants, particularly for the higher paraquat strength products. However, there is a thermodynamic rationale for this to be the case. The surfactants are designed to disperse and spread the active on the plant surface. Acid-triggered gelling is designed to slow the dispersion of the formulation in the aqueous environment of the stomach. Furthermore, surfactant molecules de-lipidise and can damage biological membranes. This effect allows the more polar molecules like paraquat to gain access to cells. Indeed, many surfactants are classified as irritants in their own right for this reason. INTEON technology is designed to protect the gastrointestinal mucosa and to slow the dispersion and absorption of the ingested paraquat product. On this basis you might expect INTEON technology to work better in surfactant-free systems. More studies will help to see if this is really the case.

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