

Subject: RE: Minutes EPMF-STF meeting 5th July
Date: Friday 13 July 2018 at 09 h 57 min 08 s Central European Summer Time
From: Hindle, Stuart (S)
To: Watt, Ian, Katrien Arijs, Andrew Goodyear
CC: Jelle Mertens, CAPON France
Attachments: image001.png, Arts et al 2018.pdf

Hello Katrien,

I discussed with Ian the proposed testing for silver acetate including the microbiome studies and I thought my recent experiences of RAC discussions around reproductevelopmental toxicity of another substance might be informative.

I attended discussions at RAC for a chelating agent, DTPA which we argued exhibits developmental effects that are non-specific and secondary to depletion of zinc. We provided significant evidence that this mechanism was the only way by which DTPA could exert its effects since supplementation with zinc in the diet negated all toxicity observed and further studies in animals fed zinc depleted diets led to similar developmental effects (in the absence of DTPA). In the end RAC concluded that the substance should be considered a Cat 1B developmental toxicant since the MOA was relevant for humans and the secondary effect was not non-specific. I attach a copy of our recent publication on the matter which describes in more detail the significant body of evidence we presented.

A couple of learnings I take away from the experience are, overall RAC are very conservative, reproductevelopmental effects even in the presence of significant maternal toxicity (i.e. death) will result in default Cat 2 classification according to current guidance interpretation and cause and 'secondary' effect must be unequivocally demonstrated to avoid category 1B classification.

In that context I wonder whether the intention to perform microbiome studies to argue or demonstrate that any effect of silver would be secondary to disruption of the microbiome would be sufficient enough to avoid more stringent classification. RAC for instance could argue that the effects occur in parallel and that such effects are not severe enough to negate classification in category 1B. I would therefore suggest that more robust evidence would need to be provided concerning overall MOA and would urge that additional investigations be included in the intended studies to demonstrate the secondary, non-specific nature of the reproductevelopmental effect.

I am of course happy to discuss this further with you and happy to review any proposals made and provide my thoughts and input.

Please don't hesitate to contact me if you have any questions.

With best wishes and kind regards,

Stuart

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