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**From:** [Redacted]  
**Sent:** 7/29/2015 11:51:31 PM  
**To:** HEYDENS, WILLIAM F [Redacted]  
**CC:** FARMER, DONNA R [Redacted]  
**Subject:** Charge!!!!

Bill and Donna,

Thanks so much for replying to my questions on charge questions. I know it was a very busy day for you guys and I really appreciate your time on this.

Please see below for a draft of charge questions for genotoxicity and oxidative stress. I can incorporate these into a process document but it's my understanding the charge questions themselves are high priority. Of course, I want to make sure these will provide answers to all key questions of interest. I think that asking the panel to respond to IARC's conclusions is actually pretty useful focus for questions and helps ensure that key points are addressed.

Any changes are more than welcome. I suggest sending draft charge questions and suggested process to the panel members (genetic toxicology panel that is) before any needed final review. After some thought I decided that trying to address oxidative stress indirectly as part of genotoxicity didn't really work as well as addressing it as a separate mechanism because IARC treats it as a separate mechanism from genotoxicity and makes important conclusions about oxidative stress as a separate mechanism. However, we need to make sure the panel feels comfortable addressing oxidative stress because I don't think that wasn't presented to them.

I will work on the rest of the draft process document tomorrow morning.

Thanks.

[Redacted]

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**Genetic Toxicology and Oxidative Stress Panel Charge Questions:**

**Genotoxicity**

What is the overall weight of evidence evaluation for genotoxicity and DNA-reactive genotoxicity of glyphosate, glyphosate-based formulations (GBF's) and aminomethylphosphonic acid (AMPA)? [This could be refined by discussing endpoints, test system phylogeny and mechanisms as separate elements of genotoxicity evaluation].

Does the panel agree with IARC's conclusions that there is strong evidence that glyphosate causes genotoxicity, strong evidence for genotoxicity of GBF's and moderate evidence for genotoxicity of AMPA?

### **Oxidative Stress**

What is the overall weight of evidence evaluation for oxidative stress induction by glyphosate, GBF's and AMPA? [This would include evaluation of phylogenetic and exposure aspects of data, e.g. evidence whether oxidative stress is induced *in vivo* in mammals and at what dose levels].

Is induction of oxidative stress a plausible explanation for non DNA-reactive genotoxic effects observed in some genotoxicity studies?

Does the panel agree with IARC's conclusion that there is strong evidence that glyphosate, GBF's and AMPA can induce oxidative damage? [As above, this could include perspective on phylogenetic and exposure considerations]

### **Cancer Mechanisms**

What is the overall weight of evidence that genotoxicity or oxidative stress of glyphosate or GBF's might be a mechanism for carcinogenesis in experimental animals or humans?

Does the panel agree with IARC's rationale statement that "There is strong evidence that glyphosate can operate through two key characteristics of known human carcinogens and that these can be operative in humans." and that this supports their overall evaluation that glyphosate is *probably carcinogenic to humans*. [This statement is supported in the IARC monograph by reference to "human *in vitro*" and experimental animal genotoxicity studies and by reference to the findings of Bolognesi et al. (2009) of *in vivo* human genotoxicity and by oxidative stress studies of "humans *in vitro*", experimental animals, other species and experiments showing that antioxidants decrease glyphosate oxidative stress effects]