

Message

From: HEYDENS, WILLIAM F [AG/1000] [/O=MONSANTO/OU=NA-1000-01/CN=RECIPIENTS/CN=230737]
Sent: 12/8/2010 10:17:48 PM
To: SALTMIRAS, DAVID A [AG/1000] [/O=MONSANTO/OU=NA-1000-01/CN=RECIPIENTS/CN=DASALT]
Subject: FW: Updated glyphosate activities presentation for Friday's CPTLT meeting
Attachments: Glyphosate Toxicology Activities #2.pptx

David,

I took a quick look and have a few comments in deck in red font. Let me know if you have any questions.

Also, add page numbers and "Monsanto Company Confidential" to slide deck.

Bill

From: SALTMIRAS, DAVID A [AG/1000]
Sent: Wednesday, December 08, 2010 11:17 AM
To: HEYDENS, WILLIAM F [AG/1000]
Subject: Updated glyphosate activities presentation for Friday's CPTLT meeting

Bill,

Updated and attached for your comment.

Thanks,

David Saltmiras, Ph.D., D.A.B.T.
Toxicology Manager
Regulatory Product Safety Center
Monsanto
ph ([REDACTED]

UNITED STATES DISTRICT COURT
NORTHERN DISTRICT OF CALIFORNIA

TRIAL EXHIBIT 312

Case No. 3:16-cv-0525-VC

Date Entered _____

By _____
Deputy Clerk


MONGLY02067858

Glyphosate Toxicology Activities Supporting Registration Reviews

David Saltmiras, PhD, DABT
CPTLT December 10, 2010



Overview

- Pending glyphosate regulatory reviews
 - Expert engagement
 - Testing – voluntary and mandatory
 - Publications– positioning ourselves with strong science against emotive research and politically pressured regulatory reviews
 - Political Science
- 

Glyphosate Registration/ADI Reviews

- EU Annex I Renewal
 - May 2012 dossier submission
- US EPA / Canada PMRA Registration Review
 - DCIs issued
- Japan ADI review
 - ~~on hold~~ Ongoing
 - MON data ADI = 0.75 mg/kg/day; Syngenta's = 1 mg/kg/day
- Brazil – formulation registrations & ADI review.....
- Regulators are increasingly more concerned with allegations arising in peer reviewed literature
- More balanced peer reviewed publications are needed to place poor science in context



EU Expert Panel

- EU Expert Panel established in mid 1990's to provide guidance from recognized experts in toxicology, pathology and epidemiology
- Recommended voluntary glyphosate testing strategies and scientific publications to support glyphosate regulatory reviews/ approvals and freedom to operate
- Funding to maintain a similar South American network of experts was withdrawn earlier this decade

EU Expert Panel Recommendation 1

Affirmed MON Study Proposal

- Evaluation of rat salivary gland hypertrophy
 - Arguably a driver in EU endpoint selection , ADI 0.3 mg/kg/day
 - Driver in JMPR (2004) endpoint selection , ADI 1.0 mg/kg/day
- JMPR (2004) determined salivary gland hypertrophy “of unknown toxicological significance”
 - Hypothesis of local oral irritation due to an organic acid in diets causes an adaptive response in rodents
- 8-week rat study
 - Dietary citric acid (low pH), sodium citrate (high pH) and gavage citric acid (bypassing oral cavity) Vs diet and gavage controls



Salivary Gland Study Results

- Statistically significant increase in parotid salivary gland weight in the low pH diet group
- Cytoplasmic alteration in the parotid salivary glands was most severe in the low pH diet group
- Considered an adaptive response rather than an adverse effect
- Future publication planned
- Opens opportunity to argue for increased glyphosate ADI in the European Union Again

EU Expert Panel Recommendation 2

- Context of two *In vitro* publications by the group
 - Gasnier et al. (2009), *Glyphosate-based herbicides are toxic and endocrine disruptors in human cell lines*
 - Benachour et al. (2009), *Glyphosate Formulations Induce Apoptosis and Necrosis in Human Umbilical, Embryonic, and Placental Cells*
- Professor , Uni. of Birmingham, UK
- Comparison of R400 and R400 formulation blank cytotoxicity to that of widely used generic detergents
 - Sodium dodecyl sulphate (SDS) – anionic detergent
 - Benzalkonium chloride (BC) – cationic detergent
 - Biosoft N-25 – non-ionic detergent

In Vitro Cytotoxicity Findings

- R400 and R400 blank have very similar toxicity profiles
 - Seralini assertion of “enhanced” glyphosate toxicity from surfactants is debunked; no synergistic effects
- R400 cytotoxicity data are repeatable
- Cell lines tested perform fairly similarly – suggests a non specific effect
- Rank order of cytotoxic potency
 - BC (cationic) > Biosoft (non-ionic) > SDS (anionic) ~ R400 = R400 blank
- Evidence that serum is protective as expected
 - stressed the *in vitro* systems with absence of serum
- Future publication(s) planned

THIS SLIDE HAS NOTHING TO DO

WITH REST OF DECK Testing – mandatory

- Immunotoxicity – US EPA Data Call In
 - In life complete and no issues
 - Immunoassay results due next week
- – US EPA Program
 - Test Orders: 11 “Screening” assays @ \$1,000,000
 - OSRI Review: likely EPA rejection by end 2010
 - Head of retiring this year
 - Talk of industry law suit through the Endocrine Policy Forum
 - Coordinate testing through JGTF ToxTWG



Publications

- Williams et al. (2000) an invaluable asset
 - Monsanto responses to agencies
 - Scientific Affairs rebuttals
 - Regulator reviews
- More current external expert publications are now needed to support our FTO and Registration Reviews
 - EU Annex 1 Renewal requires extensive lit. review
 - Will weight of evidence be measured by number of publications or quality of the science???



Third Party White Papers

- Often critique methodology, interpretation of data and context of findings
- Kept in “back pocket”
- Response to Romano et al. (2010) *Prepubertal exposure to commercial formulation of the herbicide glyphosate alters testosterone levels and testicular morphology*
 - Exponent: Bill Kelce, Jim Lamb and John DeSesso
- Response to Bolognesi et al. (2009) *Biomonitoring of Genotoxic Risk in Agricultural Workers from Five Colombian Regions: Association to Occupational Exposure to Glyphosate*
 - Larry Kier



Publications in the works

- Letter to the Editor of Chemical Research in Toxicology
 - Carrasco publication; Paganelli et al. (2010) *Glyphosate-Based Herbicides Produce Teratogenic Effects on Vertebrates by Impairing Retinoic Acid Signaling*
 - Currently undergoing internal Monsanto review
 - HARC Letter to Editor addressing industry data integrity
- Jack Mandel – epidemiology cancer endpoints currently in peer review
- Jack Mandel – epidemiology non-cancer endpoints
- John DeSesso – reproductive and developmental toxicity and endocrine disruption, final Monsanto review next week
- Adaptive responses of the salivary glands to an acidic diet. Eurotox presentation and manuscript for publication

Proposed Publications – funding?

- [redacted] – independent review of Agricultural Health Study (epidemiology) for rebuttals to claimed associations of health effects with glyphosate exposure
- Epidemiology methods paper – to provide a concise reference for critique of poor epidemiological methods
- [redacted] – *in vitro* cytotoxicity evaluations of surfactants. Eurotox presentation and manuscript for publication

Proposed Publications cont.

- Larry Kier – Glyphosate genotox overview (post-2000)
 - Note: is on the EFSA Scientific Panel on Plant Protection products and their Residues (PPR Panel)
 - The Panel works closely with the Pesticide Risk Assessment Peer Review (PRAPeR) which is responsible for the EU- peer review of active substances used in new or existing plant protection products.
 - <http://www.efsa.europa.eu/en/ppr/aboutppr.htm>
- – *in vitro* exposures and the relevance to human health risk assessment. Evaluating published doses Vs human serum levels
- – dietary exposure assessment for European regions



Political Science

- Unfortunately, we are facing regulatory reviews with increased focus on
 - Claims in the peer reviewed literature, irrespective of the quality of the science
 - Stakeholder input including activist researchers
 - Political pressure on outcomes – e.g. POEAs in Germany
 - Reduced pesticide use in general
- Williams et al. (2000) has served us well in toxicology over the last decade
- We need a stronger arsenal of robust scientific papers to support the safe use of our products as we face the next set of chemistry registration reviews across the globe
- With increasing business interests in South America, a local network credible expert scientists is crucial to facilitate scientifically robust and objective regulatory evaluations of our products *We have not determined exactly what we should & could do here. I would modify bullet to reflect that we need to determine an appropriate & do-able (i.e., we can get someone to pay for it course of action here*