NTP
National Toxicology Program

Glyphosate Research Scoping

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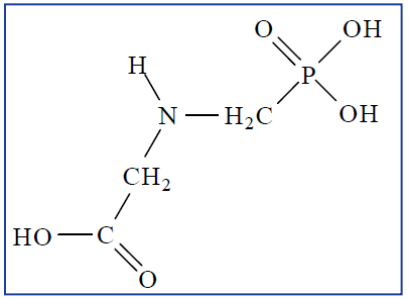
NTP Board of Scientific Counselors Meeting
June 15 – 16, 2016

Glyphosate

A heavily used herbicide

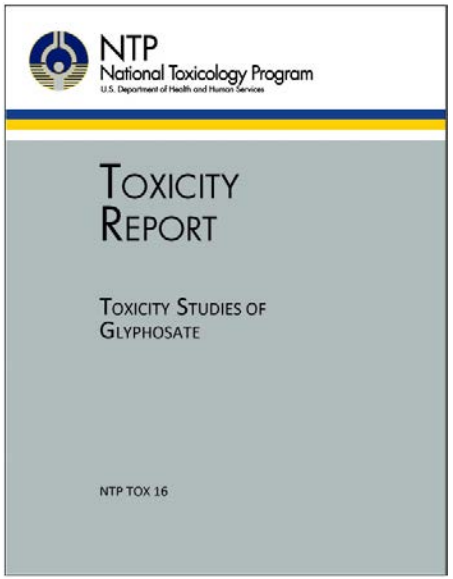


CASRN 1071-83-6

- High production herbicide registered in 130 countries, manufactured by at least 91 producers in 20 countries
  - > 1.7 million tons applied in USA from 1974 – 2014 (~90% for agriculture)
  - Total global use ~ 9.4 million tons from 1974 – 2014
  - More than 750 products containing glyphosate are available in USA alone
- Post-emergent, systemic, non-selective herbicide by targeting an amino acid synthesis pathway that is present in plants and bacteria but not in mammals
- Applied as a mixture of glyphosate and spray adjuvants to improve delivery of glyphosate to plants
- General population exposed through diet & use of consumer products

Toxicity Report No. 16: 13-week study with glyphosate in feed (1992)

- Nominated by California Regional Water Quality Control Board North Coast Region (1981)
- NTP selected glyphosate for toxicity evaluation because of:
  - Expanding use
  - Potential for human exposure
  - The lack of published reports concerning comprehensive toxicity or carcinogenicity evaluations



Toxicity Report No. 16: 13-week study with glyphosate in feed (1992)

- Top dose for rats ~3,400 mg/kg/day (males & females)
  - No gross lesions at necropsy
- Top dose for mice ~10,800 and ~12,000 mg/kg/day (males & females, respectively)
  - No gross lesions at necropsy
- Micronucleus assay was negative in male and female mice (also 13-week exposure via feed)
- Bacterial mutagenicity tests were negative
- ADME studies indicated low absorption and rapid elimination

Is glyphosate a carcinogenic risk for humans?

Current assessments

IARC Monograph 112: Glyphosate is “probably carcinogenic to humans”

Joint FAO/WHO Meeting on Pesticide Residues (JMPR): Glyphosate is “unlikely to pose a carcinogenic risk to humans via exposure from the diet”

European Food Safety Agency (EFSA): Glyphosate is “unlikely to pose a carcinogenic hazard to humans”

In progress…

US EPA: Completing a new risk assessment for re-registration of glyphosate; prior classification “evidence of non-carcinogenicity for humans”

Different analyses for different purposes

Key differences

- Hazard identification versus risk assessment
  - IARC evaluates whether a chemical is a cancer hazard
  - JMPR evaluates potential cancer risk from dietary exposure
  - EPA and EFSA perform mandated, comprehensive risk assessments with cancer as one of many endpoints
- Access to unpublished, industry-funded guideline studies that are part of pesticide registration packages is limited
  - EPA, EFSA, & JMPR have greater access to unpublished studies
- Active ingredient versus glyphosate formulations
  - IARC included glyphosate formulations in evaluation

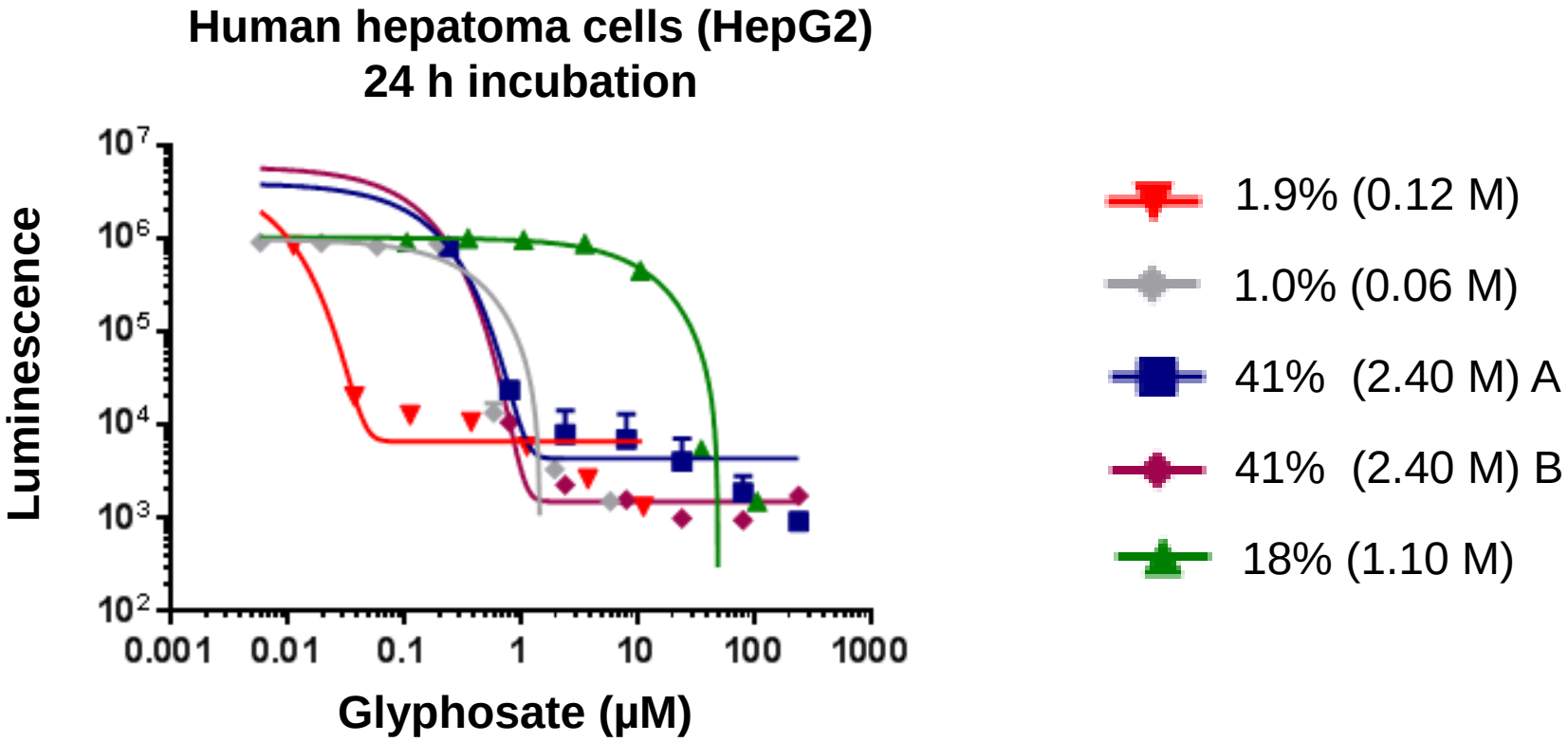
Objectives

- Compare toxicity of glyphosate versus formulations (and formulations vs. formulations)
- Provide publicly available toxicology data on cancer-related endpoints
- Provide publicly available toxicology data on non-cancer endpoints
- Investigate mechanisms of how glyphosate and formulations cause toxic effects

Toxicity of glyphosate vs. formulations

What is the role of glyphosate in the toxicity of formulations?

- Are all formulations equally toxic?
- What drives the toxicity of formulations?



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Cancer-related endpoints

10 Key Characteristics of Carcinogens

- Act as an electrophile either directly or after metabolic activation
- Genotoxicity
- Alter DNA repair or cause genomic instability
- Induce epigenetic alterations
- Induce oxidative stress
- Induce chronic inflammation
- Be immunosuppressive
- Modulate receptor-mediated effects
- Cause immortalization
- Alter cell proliferation, cell death, or nutrient supply

Smith et al. (2016) Key characteristics of carcinogens as a basis for organizing data on mechanisms of carcinogenesis. *EHP*.124(6): 713-21

Publicly available data

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Non-cancer related endpoints

- Screening-level analysis of literature using SWIFT
  - Sciome Workbench for Interactive, Computer-Facilitated Text-mining (SWIFT) software
  - Identify and rank research that is most relevant to questions
  - Categorize by exposure, outcome, and evidence stream
  - Visualize and summarize
- Describe evidence base for health outcomes investigated in connection to glyphosate exposure (and by definition also what has not been investigated)

Howard et al. (2016) SWIFT-Review: a text-mining workbench for systematic review. *Systematic Reviews*, 5(1):87

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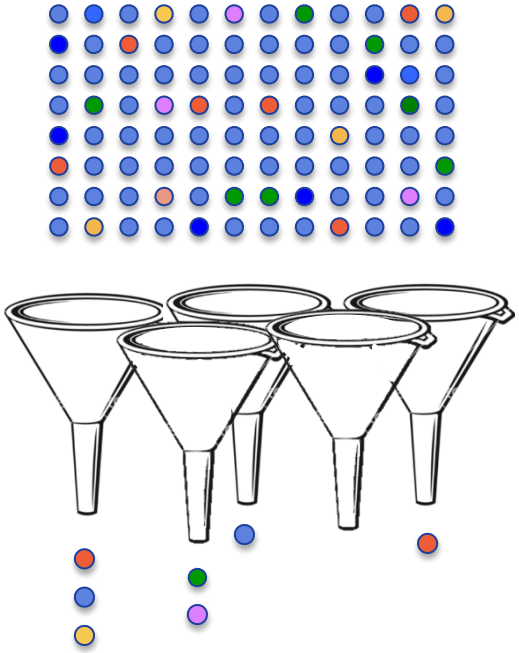
Toxicity of glyphosate & formulations

Approach – rapid screening & short-term *in vivo* tests

Rapid screening of glyphosate & formulations



Short term *in vivo* testing:

Guideline genotoxicity assays
Gene expression assays
Assays for oxidative stress

Robust dose-response data to aid risk assessment

Objectives

- Tailor research program to match decision-making time frame

Questions for BSC

- Comment on the relevancy of the proposed activity relative to the mission and goals of the NTP.
  - *The NTP's stated goals are to: Provide information on potentially hazardous substances to all stakeholders; Develop and validate improved testing methods; Strengthen the science base in toxicology; Coordinate toxicology testing programs across DHHS (http://ntp.niehs.nih.gov/go/about).*
- Comment on whether the steps outlined in the presentation to formulate the research problem and for gathering input are appropriate.
- Provide any other comments *e.g.* on rationale, scope, significance that you feel NTP staff should consider in developing this activity.