Talking Points on the IARC Assessment of Glyphosate Published Online in *Lancet Oncology*, March 20, 2015

"There was limited evidence in humans for the carcinogenicity of glyphosate. Case-control studies of occupational exposure in the USA, Canada, and Sweden reported increased risks for non-Hodgkin lymphoma that persisted after adjustment for other pesticides"

- Monsanto does not believe there is credible epidemiologic evidence that glyphosate use can cause non-Hodgkin lymphoma (NHL) because the largest and single most important study (see details immediately below) that evaluates the health of pesticide applicators (the Agricultural Health Study, AHS) found no link
    - In fact, the co-investigator of the AHS in 2008 reported the findings to date to the Presidents Panel on Cancer - no cancer sites were associated with glyphosate
- Epidemiology experts with whom we have consulted believe that the results of the AHS dwarf (and 'trump') those of the much smaller case-control studies and support the conclusion that there is no credible evidence that glyphosate can cause NHL
- Case-control studies, like those cited by IARC, are well known to be prone to a number of biases, especially enhanced recall exposure by individuals who have experienced a dramatic life event (cancer diagnosis)
- In the recent EU renewal evaluation (2015), the German regulatory authorities reviewed these 3 case-control studies, the De Roos *et al.*, 2005 as well as many other epidemiology studies, and they concluded:
    - "In epidemiological studies in humans, there was no evidence of carcinogenicity and there were no effects on fertility, reproduction and development or of neurotoxicity that might be attributed to glyphosate."
- And previously in 2004, the World Health Organization (JMPR/WHO) concluded:
    - "Widely used pesticides, like glyphosate, have recently become a focus of epidemiological research. In the past few years several epidemiological studies have been published that reported weak associations of glyphosate with lymphopoeitic cancers "
    - "However, the results of these studies do not meet generally accepted criteria from the epidemiology literature for determining causal relationships. Generally, the associations were rather weak and rarely statistically significant. Control for potential confounding factors, including other pesticides, was not possible owing to limited available information and small numbers of subjects. It was not measured whether there actually was any internal exposure or the extent of such exposure and, accordingly, a possible dose–response relationship could not be evaluated."

"The AHS Cohort did not show a significantly increased risk of non-Hodgkin lymphoma"

- Again, the epidemiology experts with whom we have consulted believe that the results of the AHS supercede those of the much smaller/weaker case-control studies and support the conclusion that there is no credible link between glyphosate use and NHL
- It is surprising and disappointing that IARC chose to discount the significance of this much more powerful study relative to the much weaker case-control studies
- The AHS study was set up in the 1990s to provide a large, unbiased set of data to examine cancer and other health risks in pesticide applicators
- To demonstrate just how large the AHS study is, the Ag Health study reported 54,315 participants the last time they published their results on glyphosate (De Roos *et al.*, 2005); this is in striking contrast to the much smaller case-control studies cited by IARC to support their claim of 'limited evidence':
    - Canada study (McDuffie et al., 2001) with 2,023 participants
    - USA study (De Roos et al., 2003) with 2,583 participants
    - Sweden study (Eriksson et al., 2008) with 2,011 participants
- Results from the AHS study showed:
    - there was no greater risk of NHL in all applicators when compared to State cancer incidence rates (Koutros *et. al.*, 2010)
    - No greater risk of NHL in glyphosate users compared to non-users (De Roos *et. al.*, 2005)
    - NHL risk did not increase with the amount of glyphosate use (De Roos *et. al.*, 2005)

"In male CD-1 mice, glyphosate induced a positive trend in the incidence of a rare tumour, renal tubule carcinoma."

- This study has been reviewed by several expert scientists/pathologists (including a formal Pathology Working group) and numerous regulatory agencies around the world, and all have concluded there is no evidence of carcinogenicity
- Furthermore, there was no increase in this tumor type in 4 other mouse studies

"A second study reported a positive trend for haemangiosarcoma in male mice.[15]"

[Ref. 15 is WHO/FAO, 2004 Joint FAO/WHO Meeting on Pesticides.]

- The results and conclusions were misrepresented by IARC
- In the actual FAO/WHO document cited by IARC, it is clearly stated:
    - "In conclusion, administration of glyphosate to CD-1 mice for 104 weeks produced no signs of carcinogenic potential at any dose."
- This conclusion was based on the following considerations pointed in the FAO/WHO review:
    - "Owing to the lack of a dose-response relationship, the lack of statistical significance and the fact that the incidences recorded in this study fell within the historical ranges for controls, these changes are not considered to be caused by administration of glyphosate."

- Further, this study has been reviewed by numerous regulatory agencies around the world, and all have concluded there is no evidence of carcinogenicity

"Glyphosate increased pancreatic islet-cell adenoma in male rats in two studies."

- Please see larger Animal Carcinogenic Data document

"A glyphosate formulation promoted skin tumours in an initiation-promotion study in mice"

- This study does not show that glyphosate has carcinogenic potential
- Fourteen well-conducted chronic studies have been done with glyphosate in rats and mice, and none of them have shown carcinogenic potential
- The most logical explanation for the results reported is that it is an artifact of the way in which the test material was administered in this particular study
- Doses in this study are not representative of human exposures to glyphosate-based formulations
- Mice received topical applications of concentrated glyphosate formulated product three times per week for 32 weeks without washing
    - This is an exposure scenario/regimen that is not relevant to humans
- Glyphosate has very low dermal absorption, and is non-volatile; thus, it would likely accumulate on mouse skin. The surfactant is non-volatile and would build-up too.
- The surfactant used in this formulation is irritating upon prolonged exposure
- Given the repeated exposure to an irritating material which is not washed off over the course of 32 weeks, the tumor promotion is likely a physical response to substantial localized dermal irritation over a prolonged period of time.
    - It is a well established toxicological phenomenon that prolonged cellular irritation/destruction from various sources can lead to increased cell proliferation and ultimately tumor formation
- Epidemiological studies reported elsewhere note no association with glyphosate and either skin or lip cancers

"Glyphosate has been detected in the blood and urine of agricultural workers, indicating absorption."

- This statement by itself is uninformative and needs to be put into context
- A science-based weight-of-evidence evaluation to determine a substance's carcinogenic potential examines human data, animal data, and exposure information – the exposure data for glyphosate argues strongly against the plausibility that glyphosate causes NHL in pesticide applicators or the general public
- When ingested, only 20-30% of glyphosate is absorbed, it is not metabolize and is

rapidly eliminated primarily unchanged from the body

- The dermal penetration of glyphosate as the formulated product is very low (<1% of that applied)
- Thus, it is not surprising that the best and most comprehensive biomonitoring exposure study of famers and their families have shown extremely low levels of glyphosate in their urine (Acquavella et. al., *Environ Health Perspec* 112:321-326, 2004)
    - The highest single value observed was 233 ppb, which gives an estimated systemic dose of 0.004 mg/kg
    - The geometric mean (GM) concentration for all farmers was 3 ppb, which correlated to a GM systemic dose of 0.0001 mg/kg
    - To put these numbers in perspective, the U.S. EPA reference dose (not likely to cause harmful effects during a lifetime) is 2 mg/kg/day, so they are 500 – 20,000 times lower than that
- Scientists from the German Federal Institute for Risk Assessment recently published a critical review of glyphosate findings in human urine samples (Niemann *et. al.*, 2015)
    - They found that only "traces" of glyphosate were found in human urine
    - They stated:
        - "It is not surprising that certain amounts can be detected in human urine samples."
        - "However, if the estimated exposure is clearly below science-based trigger values (i.e., the ADI or AOEL), there is no health concern for consumers."
        - "The conclusion can be drawn that no health concern was revealed because the resulting exposure estimates were by magnitudes lower that the ADI or the AOEL."
        - "Thus, the results of this review of urine analysis data confirm the conclusion drawn during re-assessment of glyphosate (EFSA, 2014) that the dietary intake as well as occupational exposure is unlikely to present a public health concern."

"One study reported increases in blood markers of chromosomal damage (micronuclei) in residents of several communities after spraying glyphosate formulations"

- This is a study that attempted to evaluate possible DNA damage in people living near areas where glyphosate was used aerially to eradicate illegally
- It is extremely difficult to draw meaningful conclusions from this study because there were so many uncontrolled variables and problems that come with such a study, most notably, self-reporting (inaccuracies and/or information can't be verified)
- There are various inconsistencies in this study that raise significant questions; for example:
    - The degree of DNA damage observed immediately after the glyphosate spraying was not consistent with the application rates used

    - there was no association between self-reported direct contact with eradication sprays and DNA damage in two sprayed regions
    - The largest increase in DNA damage was reported in the region where only 1 of 25 people from this population self-reported contact with spray exposure
- The clear lack of correlations led the study authors themselves to be cautious with drawing conclusions; they made somewhat different conclusions in different places in the publication:
    - In the Abstract, they say the data suggest that damage is small and appears to be transient; the evidence indicates that the genotoxic risk is low.
    - In the Discussion, they also conclude that genotoxic damage is small and transient, and that genotoxic risk is of low biological relevance.
- A more defensible conclusion that appears to be supported by the self-reported exposure information is that this study does <u>not</u> clearly demonstrate an association between glyphosate exposure and the CBMN endpoint.

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