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Glyphosate and Roundup Proven to Disrupt Gut Microbiome by Inhibiting Shikimate Pathway

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Global Research, February 09, 2020
GMWatch 11 December 2019

Region: Europe
Theme: Biotechnology and GMO

First published and posted in GR in December 2019

Fatty liver disease and death of liver tissue were also confirmed in rats fed regulatory permitted and thus presumed safe doses of the weedkiller

The primary mechanism of how glyphosate herbicides kill plants is by inhibiting an enzyme called EPSPS, which is part of a biochemical pathway known as the **shikimate pathway.** The shikimate pathway is responsible for the synthesis of certain aromatic amino acids that are vital for the production of proteins, the building blocks of life. Thus when the synthesis of the aromatic amino acids is blocked by glyphosate inhibition of EPSPS, the plant dies.

Humans and animals do not have the shikimate pathway, so industry and regulators have claimed that glyphosate is nontoxic to humans.[1] However, some strains of gut bacteria do have the shikimate pathway, leading to much debate about whether Roundup and glyphosate could affect the gut microbiome (bacterial populations). Imbalances in gut bacteria have been found to be linked with many diseases, including cancer, type 2 diabetes, obesity, and depression.

As many species of gut bacteria do have the shikimate pathway, scientists have hypothesised that glyphosate herbicides could inhibit the EPSPS enzyme of the shikimate pathway in these organisms, leading to imbalance in the microbiome, with potentially negative health consequences. Some have proposed that if glyphosate herbicides do disrupt the gut microbiome, EPSPS inhibition will be the primary mechanism through which this occurs.

However, proof that glyphosate herbicides can inhibit the EPSPS enzyme and the shikimate pathway in gut bacteria has been lacking. But a new study has proven beyond doubt that this does indeed happen.

The study in rats by an international team of scientists based in London, France, Italy, and the Netherlands, led by **Dr Michael Antoniou** of King's College London and posted on the pre-peer-review site BioRxiv, has found that Roundup herbicide and its active ingredient glyphosate cause a dramatic increase in the levels of two substances, shikimic acid and 3-dehydroshikimic acid, in the gut, which are a direct indication that the EPSPS enzyme of the shikimic acid pathway has been severely inhibited.

In addition, the researchers found that both Roundup and glyphosate affected the microbiome at all dose levels tested, causing shifts in bacterial populations.

Levels tested were previously assumed to have no adverse effect

For the study, female rats (12 per group) were fed a daily dose of either glyphosate or a Roundup formulation approved in Europe, called MON 52276. Glyphosate and Roundup were administered via drinking water to give a glyphosate daily intake of 0.5 mg, 50 mg and 175 mg/kg body weight per day (mg/kg bw/day), which respectively represent the EU acceptable daily intake (ADI), the EU no-observed adverse effect level (NOAEL), and the US NOAEL.

The study found certain adverse effects at all doses tested, disproving regulators' assumptions that these levels have no adverse effect.

Some previous studies have also reported changes in the gut microbiome of laboratory animals exposed to glyphosate and/or Roundup. However, as they did not use the more in-depth molecular profiling techniques (multi-omics) used in the latest investigation, they failed to observe the inhibition of the shikimate pathway.

Unique comprehensive analysis

The unique aspect of the new study is that a more comprehensive analysis than ever before was carried out to see if the gut microbiome changes could affect the rats' health.

The researchers applied two levels of analysis to investigate the changes:

> 1) a metagenomics analysis, which looked at the totality of DNA in the gut and thus identified all organisms present.
>
> 2) a metabolomics analysis, which looked at alterations in biochemistry of the gut microbiome environment.

Dr Antoniou commented,

> "We are the first to use this combination of profiling by metagenomics and metabolomics to look for effects of glyphosate herbicides on the gut microbiome. Through this comprehensive multi-omics analysis, we obtained definitive results demonstrating glyphosate and Roundup impact on both the bacterial population and biochemistry of the gut microbiome."

The metagenomics analysis found that both Roundup and glyphosate affected the microbiome at all dose levels, causing shifts in bacterial populations. Metabolomics revealed that the levels of two substances, shikimic acid and 3-dehydroshikimic acid, were dramatically increased at the two higher doses in the gut of the rats fed both glyphosate and Roundup. These two acids were undetectable in the gut of control animals. This is a clear indication that the EPSPS enzyme of the shikimate acid pathway was inhibited by the glyphosate and Roundup, since if it were active, it would rapidly convert the shikimic acid to the next substance in the pathway – but that didn't happen.

Dr Antoniou said that this effect had been previously hypothesised but not proven:

> "Our study provides the first proof that glyphosate and Roundup at these regulatory permitted and thus presumed safe doses inhibit the shikimic acid

pathway in gut bacteria."

Oxidative stress

The researchers also saw other changes in the gut metabolome that were indicative of oxidative stress, a type of imbalance that can lead to mutations in DNA, damage to cells and tissues, and diseases such as cancer. Gut bacteria respond to oxidative stress by producing certain substances that combat it.[2]

Biomarkers of glyphosate exposure

Dr Antoniou said that the study has broken new ground in identifying the first ever biomarker of glyphosate exposure, which could be relevant to humans:

> "Our findings suggest that surveys of human populations should be undertaken as a matter of urgency to show if there is a correlation between levels of glyphosate and shikimate. If such a correlation is found, then shikimate levels could be used as a measure of the biological effects of glyphosate exposure."

This means it is possible to see if a certain disease in a person is associated with glyphosate exposure by looking at their faecal microbiome, though a causative link between the disease and glyphosate could not be drawn.

Furthermore, the results showed distinct changes in the profile of gut bacterial populations. Glyphosate and MON 52276 increased the levels of Eggerthella spp. and Homeothermacea spp, whilst MON 52276 also increased the levels of Shinella zoogleoides. These shifts in bacterial species, if confirmed by further studies, could also act as additional biomarkers of glyphosate and Roundup exposure.

Dr Antoniou said,

> "We see definitive and consistent changes at all doses of MON 52276 and glyphosate. So even at the ADI (Acceptable Daily Intake, the level regulators believe can be ingested on a daily basis over the long term with no adverse effect) level we see these changes in bacterial populations. In the long term there may be health implications. Currently science does not understand enough about what the biological and health consequences of these changes might be, but the alterations are in themselves a cause for concern."

Liver damage in rats fed Roundup and glyphosate

The study also revealed that Roundup, and to a lesser extent glyphosate, damaged the liver and kidneys of the rats, even over the relatively short study period of 90 days. Histopathological (microscopic) examination of the liver showed that the two higher doses of Roundup caused a statistically significant and dose-dependent increase in lesions, fatty liver disease changes, and necrosis (death of tissue).

In the new study, in the glyphosate treatment group, there was also an increase in the incidence of this liver damage but it was not at a statistically significant level. In contrast, none of the control animals showed the same liver effects, so the changes in the

glyphosate-fed animals may be biologically significant. As the authors state, it's possible that they didn't reach statistical significance because the numbers of animals were too low and the exposure duration too short. Another month or two added to the study duration could have resulted in statistical significance for the glyphosate as well as the Roundup effects.

The fatty liver disease findings confirm and extend the observations of an earlier study from Dr Antoniou's team. In this previous study, rats were given a dose of Roundup that was a staggering 125,000 times lower, based on the dose of glyphosate, than the lowest dose group in the new investigation. However, they were fed this dose over a longer-term period of two years. This lower dose also caused fatty liver disease.

> "We now know that a lower dose of Roundup over a longer time or a higher dose over a shorter time produce the same outcome," said Dr Antoniou.

Kidney dysfunction

There were clear increases in kidney dysfunction – lesions, mineralisation and necrosis – in the Roundup and glyphosate groups, but they were mostly not statistically significant. This again may be because there were too few animals or the study was too short. Anyone wishing to replicate these effects in other studies should extend the length of the study and use larger numbers of animals to see if serious harm to the kidneys occurs over the long term.

Blood biochemistry

The researchers expected the signs of damage to liver and kidney function in the Roundup groups and to a lesser extent in the glyphosate groups to be reflected in the blood biochemistry. Surprisingly, however, they saw little change on this level. Dr Antoniou commented,

> "While blood biochemical measurements are routinely used to assess liver or kidney dysfunction in humans, they are relatively crude methods which could miss effects from pesticides. And so it proved in our study.
>
> "But by using 'omics' that analyse hundreds of measurements, we did see liver toxicity from glyphosate and Roundup. We saw all these changes after just 90 days of feeding at levels that regulators say produce no adverse effect.
>
> "Our study shows that more superficial physiological and biochemical measurements do not go deep enough. We must use cutting edge multi-omics methods of analysis as part of the risk assessment process, to ensure that we don't miss anything of significance for public health."

Thus far, regulators have not incorporated these methods into the risk assessment process.

New mechanism for glyphosate-cancer link?

In 2015 glyphosate was classified as a probable carcinogen by the International Agency for Research on Cancer (IARC). The agency's experts identified oxidative stress and genotoxicity (damage to DNA) as possible mechanisms.

The new study proposes a new mechanism through which exposure to glyphosate-based herbicides can cause cancer. Animals fed Roundup and glyphosate showed elevated levels of shikimic acid in their gut. Shikimic acid can have many different biological effects, including protecting the body from oxidative stress. But it has also been proposed as a cancer promoter, and a recent study found that shikimate can stimulate proliferation of human breast cancer cells. The authors state in their paper,

> "The novel mechanism of action of glyphosate on the gut microbiome we describe in the study presented here might be of relevance in the debate on glyphosate's ability to act as a carcinogen."

Power of multi-omics

In their paper, the authors explain that their study "demonstrates the power of using multi-omics molecular profiling to reveal changes in the gut microbiome following exposure to chemical pollutants that would otherwise be missed using more standard, less comprehensive analytical methods".

The researchers identified the first biomarker of glyphosate effects on the rat gut microbiome, namely a marked increase in shikimate and 3-dehydroshikimate, which indicates inhibition of the EPSPS enzyme of the shikimate pathway. In addition, they found increased levels of certain substances suggestive of a response to oxidative stress. They also showed that Roundup and glyphosate caused distinct changes in the profile of the gut bacterial populations, which could also act as additional biomarkers of glyphosate and Roundup exposure.

The researchers concluded,

> "Although more studies are needed to understand the health implications of glyphosate inhibition of the shikimate pathway in the gut microbiome, our findings can be used in environmental epidemiological studies to understand if glyphosate can have biological effects in human populations."

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Notes

1. In the Final addendum to the Renewal Assessment Report on glyphosate (October 2015), p23, rapporteur Member State Germany and co-rapporteur Member State Slovakia state, based on industry claims, "Action at the shikimic acid pathway is unique to glyphosate and the absence of this pathway in animals is an important factor of its low vertebrate toxicity."

2. Increased levels of γ-glutamylglutamine, cysteinylglycine and valylglycine were found in the gut.

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