Roundup causes non-alcoholic fatty liver disease at very low doses

Cutting edge molecule profiling analyses reveal that the popular weedkiller Roundup causes liver damage at doses permitted by regulators

A new peer-reviewed study led by Dr Michael Antoniou at King's College London using cutting edge profiling methods describes the molecular composition of the livers of female rats administered with an extremely low dose of Roundup weedkiller over a 2-year period. The dose of glyphosate from the Roundup administered was thousands of times below what is permitted by regulators worldwide. The study revealed that these animals suffered from non-alcoholic fatty liver disease (NAFLD). The study is unique in that it is the first to show a causative link between consumption of Roundup at a real-world environmental dose and a serious disease condition.

Background to current study

1. A previous study involving administration of Roundup weedkiller to rats was conducted by Gilles-Eric Seralini and colleagues.
2. This original investigation administered an extremely low, environmentally relevant dose of a commercial Roundup formulation at 0.1ppb (parts per billion)/50ppt (parts per trillion) glyphosate via drinking water for 2 years. Daily intake of glyphosate from the Roundup was 4 nanograms per kilogram of body weight per day**,** which is thousands of times below what is permitted by regulators (Seralini et al., 2014).
3. Analysis at an anatomical (organ) and blood/urine biochemical level suggested a higher incidence of liver and kidney damage in the Roundup treatment group compared to control animals. Liver and kidney pathologies were also present in the control group due to the advanced age of the animals, but at a lower frequency. (Seralini et al., 2014)
4. A follow up investigation of the gene function profiles of the livers and kidneys from the female animals from this same study strongly supported the observation that these organs were damaged suggesting the presence of an increased incidence of fibrosis (scarring), necrosis (areas of dead tissue), phospholipidosis (disturbed fat metabolism) and damage to mitochondria (the centres of respiration in cells) compared to control animals Mesnage et al., 2015).

Purpose of current study

We have previously reported the gene function profile (“transcriptomics”) analysis; i.e., which genes are turned off or on and at what level, in livers and kidneys from female rats fed an ultra-low dose of Roundup (Mesnage et al., 2015). Our results supported observations at an anatomical (organ) and blood/urine biochemical level that these organs suffered an increased incidence of structure and functional damage [fibrosis (scarring), necrosis (areas of dead tissue), phospholipidosis (disturbed fat metabolism) and damage to mitochondria (the centres of respiration in cells)] compared to control animals (Mesnage et al., 2015). However, although gene function profile transcriptomics analysis is able to predict health or disease status of an organ, it does not provide definitive proof of harm. This is mainly because it does not give a direct measure of the actual biochemistry of the organ under study – and also because alterations in gene function seen in a test do not always result in changes in physical composition (proteins, small molecule biochemical) that could lead to disease.

In our new study we undertook a follow-up protein composition profile (“proteomics”) and small molecule metabolite biochemical profile (“metabolomics”) investigation of the same liver samples to confirm the prediction of disease suggested by our transcriptomics gene expression profile analysis. **As the proteomics and metabolomics directly measure the actual composition of the organ, these analytical methods provide a definitive assessment of its health or disease status.**

Findings

Proteins significantly disturbed (214 out of 1906 proteins detected), as shown by the proteomics profiling, reflected a type of cell damage from reactive oxygen (peroxisomal proliferation), steatosis (serious fatty liver disease) and necrosis (areas of dead tissue).

The metabolomics analysis (55 metabolites altered out of 673 detected) confirmed lipotoxic (excess fatty tissue) conditions and oxidative stress. Metabolite alterations were also associated with hallmarks of serious liver toxicity.

Overall, metabolomics and proteomics disturbances showed a substantial overlap with biochemical hallmarks of non-alcoholic fatty liver disease and its progression to steatohepatosis (serious fatty liver disease) and thus definitively confirm liver dysfunction resulting from chronic ultra-low dose Roundup exposure.

Analytical methods

The cutting-edge molecular composition analytical methods used were:

(i) Metabolomics: analysis of types and amounts of small molecule metabolites or chemicals within the organ or system being studied
(ii) Proteomics: analysis of the types and levels of proteins within the organ or system being studied

These omics analyses reveal *molecular signatures* that can be used to *predict* and/or *confirm* long-term toxic effects resulting from the consumption of a chemical pollutant, in this case Roundup.

Relevance to health

These results demonstrate that long-term consumption of an ultra-low, environmentally relevant dose of Roundup at a glyphosate daily intake level of only 4 nanograms per kilogram of body weight per day, which is 75,000 times below EU and 437,500 below US permitted levels, results in non-alcoholic fatty liver disease (NAFLD). Regulators worldwide accept toxicity studies in rats as indicators of human health risks. Therefore, the results of this latest study may have serious consequences for human health.

NAFLD currently affects 25% of the US population. Risk factors include being overweight or obese, having diabetes, high cholesterol or high triglycerides in the blood. Rapid weight loss and poor eating habits also may lead to NAFLD. However, some people develop NAFLD even if they do not have any risk factors. Symptoms include fatigue, weakness, weight loss, loss of appetite, nausea, abdominal pain, spider-like blood vessels, yellowing of the skin and eyes (jaundice), itching, fluid build-up and swelling of the legs (edema) and abdomen (ascites), and mental confusion. NAFLD can progress to the more serious condition non-alcoholic steatohepatitis (NASH). NASH causes the liver to swell and become damaged. Most people with NASH are between the ages of 40 and 60 years. It is more common in women than in men. NASH is one of the leading causes of cirrhosis in adults in the United States. Up to 25% of adults with NASH may have cirrhosis. (see http://www.liverfoundation.org/abouttheliver/info/nafld/).

Quote from lead author Dr Michael Antoniou:

"*The findings of our study are very worrying as they demonstrate for the first time a causative link between an environmentally relevant level of Roundup consumption over the long-term and a serious disease - namely non-alcoholic fatty liver disease. Our results also suggest that regulators should reconsider the safety evaluation of glyphosate-based herbicides*."

The paper:

Mesnage R, Renney G, Séralini GE, Ward M, Antoniou MN. Multiomics reveal non-alcoholic fatty liver disease in rats following chronic exposure to an ultra-low dose of Roundup herbicide. *Scientific Reports*, 2016; 6:39328.

*Communicating author: michael.antoniou@kcl.ac.uk