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Study examines effects of ultra-low doses of glyphosate on gene expression profiles

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Glyphosate, often sold under the brand name of Roundup, is the world's most widely used weed-killer. While Glyphosate has approval from regulatory bodies worldwide, there are growing concerns about its possible adverse health effects. In March 2015, the World Health Organization's International Agency for Research on Cancer classified glyphosate as 'probably carcinogenic in humans'.

Surveys of populations in Europe show that most people have glyphosate in their urine. Humans ingest glyphosate residues mainly from foods including cereals (such as wheat, oats, barley, rye), which have been 'desiccated' with glyphosate-based herbicide just prior to harvest and Roundup-tolerant genetically-modified (GMO) crops like sugar beets, corn, canola (rape), and soy.

A study published in 2014 by the US Geological Survey found that across 38 US states there was glyphosate or its degradation product in most rivers, streams, ditches, and the output of water treatment plants sampled.

Dr Michael Antoniou, based at a leading London University, is using Qlucore's Omics Explorer on a series of studies looking at the effects of ultra-low doses of glyphosate on gene expression profiles (transcriptomes), protein profiles (proteomes), and small molecule metabolite profiles (metabolomes) in rats and cell cultures.

Dr Antoniou's research group employs cell and molecular analytical approaches to investigate transcriptional and post-transcriptional events that regulate gene expression including in response to various environmental stimuli, including environmentally relevant doses of key pesticides and other chemical pollutants.

The group is particularly interested in epigenetic changes (changes that become stably inherited patterns of gene function from one cell division to another) in light of evidence that even brief exposure to some chemicals, especially those able to disrupt endocrine (hormone) systems during foetal development or early life, can have a lasting effect on gene control. "Such a fixed change in gene expression pattern can lead to all kinds of problems later in life ranging from obesity, diabetes, a propensity to certain cancers and so on," explains Dr Antoniou.

Powerful visualizations show clear results

In the group's first study using the Qlucore software, post doctorate researcher Dr Robin Mesnage analyzed the transcriptomes of the livers and kidneys of ten rats treated with ultra-low, environmental doses of Roundup herbicide for two years and ten controls that hadn't. In an earlier study of the same animals, evidence of damage was found in the treated rats' urine, blood biochemistry and anatomy.

The aim was to discover whether glyphosate had changed the transcriptomes and if so, what was the nature of these changes. Principal component analysis (PCA) visualization was the first step followed by heat map visualizations and statistical analysis.

As Dr Antoniou explains:

> Rats have around 28,000 genes, only a subset of which will be switched on in the liver and in the kidney. Each gene is a dimension of analysis so you have 28k variables, which you need to reduce to something manageable.
>
> Using a PCA visualization, Qlucore allows you to graphically represent all these variables in just three dimensions, so that each animal occupies a particular location. Very quickly you can see how each animal relates to another and any treatment-related effect. If a number of animals are clustered together, you know that the effect is the same.

PCA charts can be output as video files and rotated in 3D. "It is really powerful because sometimes by rotating the plot, you can see correlations that are not so clear in a flat 2D diagram," says Dr Antoniou.

"Heat map visualizations show the activity of each gene for each rat organ so you can see the variation in the group and whether it is homogenous." says Dr Mesnage, who has been working on Roundup toxicity for eight years.

In this transcriptome analysis, the heat map visualizations showed a clear separation of the control animals and those treated with Roundup, with massive alterations in the gene expression profile of the latter.

Predictions based on molecular 'signatures'

To gain further insight into these effects, Dr Antoniou and Dr Mesnage are hoping to use a new Omics Explorer feature called Build Classifier that can be used to make predictions based on molecular 'signatures'. "If you see an alteration in a certain pattern of gene function, you can compare that pattern to another batch of genes to see if the signature matches. By taking those alterations and looking at them collectively, you could predict over time that a certain health problem will be the outcome," explains Dr Mesnage.

If identifiable transcriptome, proteome and metabolome signatures can be found for a given dose of Roundup or other chemicals of interest, animal model studies could be completed much faster. Rats, for example, could be given low doses over a few months, rather than over two years making it possible to do larger numbers of shorter tests.

"Even though the exposure would be short, we are interested in whether we might still see an alteration in gene expression patterns in the blood, liver and kidney, even if the animal doesn't show any overt health problems," explains Dr Mesnage.

He adds:

> If the changes are from epigenetic mechanisms of gene control, we know that the signatures can become fixed. On that basis, we could predict that kidney or liver function would be compromised in the long term.

A more wide-ranging project is using Omics Explorer to analyze possible endocrine disruptive effects in the transcriptome of tissue culture cell systems, such as human breast cancer cells, treated with low doses of a range of different pesticides. "For example, if a chemical in food or water mimics the effect of oestrogen, that would be a concern for a woman with hormone dependent breast cancer," comments Dr Antoniou.

Dr Antoniou and his team hope that their herbicide and pesticide studies and those of scientists in other sectors, particularly in the field of endocrinology, will encourage regulatory agencies to update the techniques they use to evaluate chemical toxicity.

"We hope our work will further illustrate that regulators must embrace the latest principles of science that are showing potential toxicity at very low levels of exposure," concludes Dr Antoniou.

Source:
http://www.glucore.com/
