



Inconclusive Experiment with Rats

By Bill Menke, December 1, 2013

The *New York Times* recently reported the retraction of a widely-quoted 2012 research paper¹ by Séralini et al. on the toxicity of genetically-modified corn. The Times article says:

The editor of the journal, Food and Chemical Toxicology, said in a letter to the paper's main author that the study's results, while not incorrect or fraudulent, were "inconclusive, and therefore do not reach the threshold of publication."

Article² by Andrew Pollack in the NY Times.

I am familiar with the Séralini et al. (2012) paper because a friend forwarded me a copy the day after it was published. I read it but was not impressed by the statistics that underpinned the paper's main result, that rats fed genetically-modified, herbicide-resistant corn have a higher incident of cancer than rats fed unmodified corn. Here's the text of my email back to my friend:

"Researchers studied 10 groups, each containing 10 male and 10 female rats". Nine groups were fed various combinations of Roundup / NK603-maize. "The final control group was fed an equivalent diet with no Roundup or NK603 ..."

Thus, the control group contained only ten individuals of each sex.

Consider now the statement

"By the beginning of the 24th month 50%-80% of females in all treated groups had developed large tumors, with up to three per animal. Only 30% of the controls were affected."

Incidentally, doesn't 30% of control (equal "normal") rats developing large tumors strike you as high? This probably means that the rats were from a strain specifically developed to develop tumors.

Anyway, the estimated 30% of the female controls translates into 3 individuals, so the 95% confidence interval on the true rate is pretty broad, 7%-60% (based on a calculation that I just did³). Similarly, the estimated 50% rate translates into 10%-65% and the estimated 80% rate translates into 45%-97%. There is significant overlap between the confidence intervals of the true rates, so that one cannot exclude the Null Hypothesis that the true rates are all equal.

The aggregate rate for the 90 treated females is not stated, but is presumably in the 50%-80% range. Let's split the difference and guess 65%. If the estimated rate based on 90 female rats was 65%, then the 95% confidence interval for the true rate is 53%-73%. Again, the confidence interval overlaps that of the control; the difference in rates is not statistically significant.

Also, note that the 9 treated groups consisted of

- 3 given only the herbicide Roundup
- 3 given only (?) NK603-maize (the article is a bit fuzzy on that)
- 3 given both

That the herbicide is bad to eat is unsurprising. The more interesting issue is whether NK603-maize is bad to eat. But only the second group of 3 tests is relevant to that question. So making aggregate statements about all nine treated groups obscures the more interesting issue.

Email by Bill Menke, September 20, 2012

My conclusions are similar to the editor's: The results are inconclusive because the observed differences in cancer rates are not statistically significant.

One of the lessons here is that poor science is not that hard to spot. The trick is to focus on the connection between the data and the inferences drawn from those data, and to ask whether the connection is credible. Knowing a little statistics helps, too.

The NY Times article confirmed my conjecture that the strain of rats used was one with a high rate of cancer. I guess that Séralini has taken some flack over this, too, for the article cites a subsequent comment by him, to the effect that what mattered was the difference in tumor incidence between the rats fed the corn or herbicide and the controls, and not the overall rate. I tend to agree with Séralini, although I also think that not bringing attention to the special attributes of these rats was a bit disingenuous of him. I do find delicious the irony that Séralini's paper is critiquing genetically-modified corn using genetically-modified rats (although maybe the rats have been developed through traditional selected breeding as contrasted to direct gene manipulation).

My biggest concern with the paper is that its statistical weakness is inherent in its design. Any scientist would do well to ask, “What could I prove in the best-case scenario?”, before launching into lab work. Rate studies are notoriously difficult to conduct, because of the large number of individuals that need to be studied in order to accurately determine a rate. In Séralini et al.’s ten-rat study, the rate of cancer in the genetically-modified-corn-fed rats would have had to been at least twice as high as normal to be detectable. I suppose that Séralini et al. might have thought such a differential possible; after all, the rate for lung cancer in smokers⁴ is more than a factor of *ten* higher than for non-smokers. But their study had no hope of detecting, say, a 10 percent increase in cancer rate, which would still be significant from a public health perspective. Given what I know about the biochemical mechanism for herbicide resistance⁵, I feel that the likelihood of herbicide-resistant corn being a carcinogen as potent as the tobacco plant is small, but that the possibility of a smaller degree of toxicity is a possibility worth testing for.

¹Séralini, Gilles-Eric; Clair, Emilie; Mesnage, Robin; Gress, Steeve; Defarge, Nicolas; Malatesta, Manuela; Hennequin, Didier; De Vendôme, Joël Spiroux (2012). "Long term toxicity of a Roundup herbicide and a Roundup-tolerant genetically modified maize". *Food and Chemical Toxicology* **50** (11): 4221–31, 2012.

²Andrew Pollack, Paper Tying Rat Cancer to Herbicide Is Retracted, NY Times, November 28, 2013.

³Menke, W., Research Note 108: Confidence intervals for events, September 20, 2012, www.ldeo.columbia.edu/users/menke/research_notes/menke_research_note108.pdf

⁴Actually, it’s 13 time higher for women and 23 times higher for men, rates that can be determined with considerable accuracy since doctors are examining many millions of people. See Lung Cancer Fact Sheet, American Lung Association, 2013. www.lung.org/lung-disease/lung-cancer/resources/facts-figures/lung-cancer-fact-sheet.html#SmokingAttributable_Lung_Cancer

⁵Glyphosate, the active ingredient in the herbicide Roundup, kills plants by interfering with an enzyme involved in the production of an amino acid (a building block of protein) which plants need to manufacture in order to grow, but which animals get from their diet. “Roundup-ready” corn has been genetically-modified to produce a different version of the enzyme, discovered originally in bacteria, which is not as sensitive to glyphosate interference. It’s certainly within the realm of possibility that the substitution of one version of an enzyme for another might produce a plant that’s horribly carcinogenic. However this scenario seems to me to be much less likely than one in which the substitution has a milder effect. A better-designed experiment would be able to detect a more modest difference in toxicity than a factor of two.