

suggested by Ian Cope, that there is no official definition of new psychoactive substances. Goodair and colleagues claim that there is no universal definition of novel psychoactive substances, but such a definition, created by the Home Office Advisory Council on the Misuse of Drugs,² was included in the previously mentioned report from the National Programme on Substance Abuse Deaths (NPSAD).³ The weakness of the definition from the Advisory Council on the Misuse of Drugs is that it says little more than the generally accepted definition of legal highs—namely psychoactive substances that are not controlled by the Misuse of Drugs Act 1971.

We accept that deaths associated with non-psychoactive substances such as anabolic steroids should be reported along with deaths associated with substances that have been controlled for many years, but they should not be included in a table headed “novel psychoactive substances”, as shown in the NPSAD report.³

In our letter,⁴ we did not claim that the Office for National Statistics classified drugs as legal highs. Our reference to the term legal highs was aimed at media reports, as exemplified by the BBC.⁵ Furthermore, our comments concerning the classification of anabolic steroids and DNP were aimed at the National Programme on Substance Abuse Deaths, not the Office for National Statistics.

We declare that we have no competing interests.

*Leslie A King, David J Nutt
les@king.myzen.co.uk

Retired, Basingstoke, UK (LAK); and Imperial College, London, UK (DJN)

- 1 European Monitoring Centre for Drugs and Drug Addiction. Monitoring new drugs. http://www.emcdda.europa.eu/attachements.cfm/att_40149_EN_Monitoring_new_drugs.pdf (accessed April 9, 2014).
- 2 Advisory Council on the Misuse of Drugs. Consideration of the Novel Psychoactive Substances ('Legal Highs'). https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/119139/acmdnps2011.pdf (accessed April 9, 2014).

- 3 Corkery J, Claridge H, Loi B, Goodair C, Schifano F. Drug-related deaths in the UK: January–December 2012. Annual Report 2013, National Programme on Substance Abuse Deaths (NPSAD), St George's, University of London. <http://www.sgul.ac.uk/research/projects/icdp/our-work-programmes/pdfs/National%20Programme%20on%20Substance%20Abuse%20Deaths%20-%20Annual%20Report%202013%20on%20Drug-related%20Deaths%20in%20the%20UK%20January-December%202012%20PDF.pdf> (accessed Feb 14, 2014).
- 4 King LA, Nutt DJ. Deaths from “legal highs”: a problem of definitions. *Lancet* 2014; **383**: 952.
- 5 Mazumdar T. Rise in deaths from 'legal highs' in the UK. <http://www.bbc.co.uk/news/health-26089126> (accessed Feb 14, 2014).

Radiotherapy for breast cancer, the TARGIT-A trial

The TARGIT-A trial (Feb 15, p 603)¹ is a good example of trying to make data fit a pre-existing hypothesis; there are several major deficiencies in the analysis. Paramount among these deficiencies is the misuse of the non-inferiority criterion,² which requires the upper (90%) CI to be below a predefined value (here 2.5%). This criterion clearly fails when the appropriate 5-year Kaplan-Meier estimates are used, which in fact establish a 2% superiority of external beam radiotherapy ($p=0.04$) and a CI extending beyond 2.5%. Table 3 of the Article¹ uses crude rates that are substantially diluted by patients with short follow-up (only 611 [18%] patients had a 5-year follow-up). The effect is even clearer if locoregional recurrence or all recurrence is used, as in previous radiotherapy trials.³

Another common but well known danger is to focus attention on the most favourable subgroup.^{4,5} The protocol clearly states that the primary analysis population includes all randomised patients. However, the report concentrates on the prepathology group. No correction for multiple comparisons or test for heterogeneity between groups is provided, and the data available suggest that it would not be significant. More should be said about all randomised patients.

Although a small increase in recurrence with a simpler therapy might well be acceptable in many circumstances, the present attempt to argue for virtually no difference by misuse of the non-inferiority criteria, focusing on the most favourable subgroup and not including all events affected by external beam radiotherapy does not give an objective assessment of this treatment modality.

I was chairman of the Data Monitoring Committee for the TARGIT trial previously but have resigned.

Jack Czuzick
j.czuzick@qmul.ac.uk

Centre for Cancer Prevention, Wolfson Institute of Preventive Medicine, Queen Mary University of London, Charterhouse Square, London EC1M 6BQ, UK

- 1 Vaidya JS, Wenz F, Bulsara M, et al, on behalf of the TARGIT trialists' group. Risk-adapted targeted intraoperative radiotherapy versus whole-breast radiotherapy for breast cancer: 5-year results for local control and overall survival from the TARGIT-A randomised trial. *Lancet* 2014; **383**: 603–13.
- 2 D'Agostino RB Sr, Massaro JM, Sullivan LM. Non-inferiority trials: design concepts and issues—the encounters of academic consultants in statistics. *Stat Med* 2003; **22**: 169–86.
- 3 EBCTCG (Early Breast Cancer Trialists' Collaborative Group). Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10 801 women in 17 randomised trials. *Lancet* 2011; **378**: 1707–16.
- 4 Czuzick J. The assessment of subgroups in clinical trials. *Experientia Suppl* 1982; **41**: 224–35.
- 5 Czuzick J. Forest plots and the interpretation of subgroups. *Lancet* 2005; **365**: 1308.

The investigators from the TARGIT-A trial¹ claim to have established non-inferiority of intraoperative radiotherapy relative to external beam radiotherapy (EBRT) for breast cancer in terms of 5-year local recurrence. Assessment of local recurrence at 5 years by comparison of binomial proportions is appropriate only if 5-year follow-up is available for all patients, whereas only 611 of 3451 patients have reached this point.

This analysis, including the non-inferiority test statistic, is therefore unreliable. The most appropriate measure of non-inferiority given available data uses the survival analysis of local recurrence rates. Based on the