

Late Deaths among Young Women Affected by the Toxic Oil Syndrome in Spain

To the Editor:

Toxic oil syndrome (TOS) is caused by a refined aniline-denatured rapeseed oil fraudulently sold as olive oil in Spain in 1981.¹ No case occurred in other circumstances: only eosinophilia-myalgia-syndrome² shares some features with it. TOS is a generalized endotheliitis of autoimmune origin.³ Commonly it started with lung infiltrates and rash. An intermediate phase with eosinophilia, myalgia, weight loss, hepatopathy, and neurological changes appeared in about half the patients, a substantial number of whom developed persistent incapacitating peripheral neuropathy, contractures, scleroderma, and pulmonary hypertension.³ Of the approximately 20,000 persons affected in 1981, over 400 died within 18 months.

We have kept a registry of cases, originally created for administrative reasons, since 1985. Through exhaustive contacts with the victims and/or their families, we identified 1,315 registered patients who died between 1983 and 1994. Reported deaths are confirmed (and the certified causes are collected) through the registrars of the municipalities where patients lived and/or died.⁴

Compared with the general Spanish population, during 1983–1994, standardized mortality ratios (SMRs) within the TOS cohort have been consistently around 80–90, except for females under age 40. In the latter group, observed-to-expected ratios were $38/16.4 = 2.32$ in 1983–1988 and $24/15.6 = 1.54$ in 1989–1994. The low SMRs in men and in older women are unexplained. The findings in young women are a source of concern, because the long-term evolution and sequelae of TOS are unknown. In 1981–1982, incidence, readmission, and lethality rates were almost twice as high in women than in men.⁵ This difference could reflect high exposure to toxic oil.

Thus, within our program of reviewing the clinical records of TOS patients dying late after the outbreak, we gave priority to the 62 women born after 1943 who died during 1983–1994. We attributed death to TOS when the clinical records showed a *continuum* between (1) registration in 1981–1982 of a severe degree of conditions typical of the intermediate or early chronic phases of TOS, and (2) recording of incapacitating plausible consequences of those conditions early before death. These *continua* included muscular wastage due to neurological impairment evolving cachexia, and/or respiratory insufficiency and/or right heart failure, pulmonary hypertension, liver dysfunction evolving to cholestatic cirrhosis. An autopsy report was available for 33 dying women.

One of these *continua* identified 31/62 women dying before age 40 during 1983–1994. The number of women who died in 1983–1985, 1986–1988, 1989–1991 and 1992–1994, respectively, numbered 16, 10, 3, and 2. Of these, the number in each period who died before reaching age 20 was 8, 2, 0, and 0.

An additional 11 deaths were caused by malignancies (8.3 expected from Spanish mortality rates): 9 deaths were caused by trauma, 4 occurred shortly after an acute cerebrovascular accident (most likely a subarachnoidal hemorrhage), 3 were caused by AIDS, 2 occurred during the *post partum* period, 1 occurred shortly after heart surgery for a congenital condition,

and 1 was caused by sepsis. The 11 lethal malignancies included: 3 breast (one of which was diagnosed before 1981) and 2 cervical cancers, 1 cancer of the colon, 2 myeloid leukemias, 1 rhabdomyosarcoma as well as 1 brain tumor and 1 "mesenchymal" tumor (the latter two lacked histological confirmation).

These preliminary findings indicate that irreversible changes in several organs initiated in 1981 had the potential for progressing to death as late as a decade later. Nevertheless, no woman dying from TOS had undergone clinical remission before death since the onset of the disease. In this subset of TOS patients, no excess of deaths from cancer has been identified up to 1994, which provides some reassurance as for the prediction of the evolution of this hitherto largely unknown syndrome.

Manuel Posada de la Paz

Ignacio Abaitua

Benedetto Terracini

Olga Giménez

Pilar Sánchez-Porro

Carmen Gómez-Mera

Centro de Investigación sobre el Síndrome del Aceite Tóxico
Instituto de Salud Carlos III
Madrid, Spain
Sinesio Delgado, 6, 28029. Madrid
(address correspondence to: Manuel Posada de la Paz)

References

1. Tabuenca JM. Toxic-allergic syndrome caused by ingestion of rapeseed oil denatured with aniline. *Lancet* 1981;2:567–528.
2. Philen RM, Posada M. Toxic oil syndrome and eosinophilia-myalgia syndrome: May 8–10, 1991, World Health Organization Meeting Report. *Semin Arthritis Rheum* 1993;23:104–114.
3. Abaitua Borda I, Posada de la Paz M. Clinical Findings. In: World Health Organization, ed. *Toxic Oil Syndrome. Current Knowledge and Future Perspectives*, 1st ed. Copenhagen: World Health Organization Regional Office for Europe, 1992;27–38.
4. Abaitua Borda I, Kilbourne EM, Posada de la Paz M, Diez Ruiz-Navarro M, Gabriel Sanchez R, Falk H. Mortality among people affected by toxic oil syndrome. *Int J Epidemiol* 1993;22:1077–1083.
5. Grandjean P, Tarkowski S, editors. *Toxic oil syndrome: mass food poisoning in Spain*. In: Report of a WHO meeting: Madrid 21–25 March 1983. 1st ed. Copenhagen: World Health Organization Regional Office for Europe; 1984; 3–9.

The P-Value and P-Value Function

To the Editor:

In an editorial concerning the policy of this journal, Lang *et al*¹ argue that point estimates and confidence intervals should be reported whenever possible and that *P*-values should then be omitted. The first recommendation is very important, the second is unfortunate. *P*-values convey information not provided by either point estimates or a single confidence interval.

Point estimates can be calculated for a variety of epidemiologic parameters such as odds ratios, relative risks, trends, or differences in mean values between groups. A confidence interval reflects the precision in the point estimate, but it does not give a complete representation of the uncertainty, and the choice of presenting 95% rather than 90%, 99%, or 97.34%

confidence intervals is arbitrary. To obtain a more complete picture of the uncertainty, we could report multiple confidence intervals but that is impractical. Few journals would have the space for, and few readers would appreciate, several different sized confidence intervals around the same point estimate.

As an alternative, it is easy and informative to report the set of confidence intervals that include an odds ratio of one within its bounds, or in other applications, a difference or trend of zero. This is done using a *P*-value. Consider an *x*% confidence interval for an odds ratio. For $x > 1 - P$, the confidence interval will contain one; for $x < P$, it will not.² The knowledge of which confidence intervals do not cover one is an indication of how confident we can be that there is a true difference between the groups in the direction observed.

Lang *et al*¹ have wisely argued for the importance of providing point estimates and confidence intervals to describe relations between exposure and disease. Point estimates and confidence intervals for "the slope of a trend line" are only rarely seen in epidemiologic articles, so the recommendation to present those is especially valuable. This does not mean that the *P*-value should be discarded. While there is a tradition to report either a confidence interval or a *P*-value but not both, it would be unfortunate for the field of epidemiology if scientists were discouraged from presenting *P*-values side by side with 95% confidence intervals. These are complementary, and the ideal is to provide both.

Martin Kulldorff

Division of Biostatistics
Department of Community Medicine and Health Care
University of Connecticut School of Medicine
MC 6205, 263 Farmington Avenue
Farmington, CT 06030-6205

Barry Graubard

Biostatistics Branch
Division of Cancer Epidemiology and Genetics
National Cancer Institute
Bethesda, MD 20892

Ellen Velie

Nutritional Epidemiology Branch
Division of Cancer Epidemiology and Genetics
National Cancer Institute
Bethesda, MD 20892
(address correspondence to: Martin Kulldorff)

References

- Lang JM, Rothman KJ, Cann CI. The confounded *P*-value. *Epidemiology* 1998;9:7-8.
- Lehmann EL. *Testing Statistical Hypotheses*. New York: Wiley, 1959;79.

The Authors Reply:

Kulldorff and colleagues suggest that presenting only a point estimate and its associated *x*% confidence interval "does not give a complete representation of the uncertainty" inherent in the data. They call for this information to be supplemented by the addition of a *P*-value that signifies which confidence interval has the null value for the parameter of interest as one of its limits. The complete representation that Kulldorff *et al* allude to is found in the *P*-value function,^{1,2} which graphs all possible confidence intervals for an estimate. The *P*-value function (see Figure 1) can be constructed from just two values, such as the upper and lower limits of a single confidence interval, or from a point estimate and a single confidence bound. The supplemental *P*-value that they call for does not

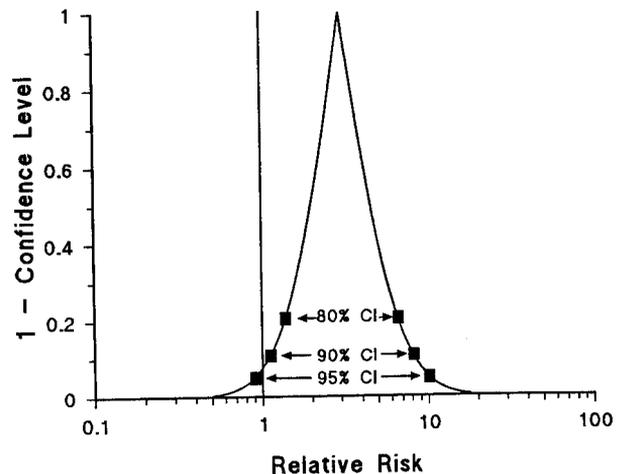


FIGURE 1. A *P*-value function for hypothetical data estimating a relative risk of 3.0, illustrating three nested confidence intervals.

add any new information about an effect estimate beyond what information is already present in the *P*-value function.

The merit of a *P*-value function is to illustrate the two fundamental elements of an estimate that are confounded in a *P*-value: the strength of the effect, and the precision of the estimate.³ Any single confidence interval by itself locates the *P*-value function on the horizontal axis, and thereby delineates the strength of the effect; a confidence interval also determines the width of the *P*-value function, which reflects the precision of the measure. Therefore any single confidence interval is sufficient to determine the complete *P*-value function. We encourage readers to picture in their minds the whole *P*-value function whenever a confidence interval is encountered, and from this, to make epidemiologically reasonable inferences that are not overly influenced by any single point on the *P*-value function, such as the null *P*-value.

Too often, epidemiologic interpretations have been distorted by imbalanced attention to statistical testing of the null hypothesis.⁴ This historical fixation is so entrenched that many students and practitioners continue to degrade the information implicit in a confidence interval by focusing on whether the null value is inside or outside the interval. Picturing the *P*-value function that corresponds to a given confidence interval is intended to upgrade rather than degrade the interpretation, by separating the strength of the relation from the precision, and showing precision as a continuous concept. Supplementing a confidence interval with the null *P*-value undermines the value of this process; not only does it not add more information, but we see it as a step backward.

Janet M. Lang

Cristina I. Cann

Associate Editors
Kenneth J. Rothman
Editor

References

- Pooler C. Beyond the confidence interval. *Am J Public Health* 1987;77:195-199.
- Rothman KJ, Greenland S. *Modern Epidemiology*, 2nd ed. Philadelphia: Lippincott, 1998;191-194.