Asbestos exposure: the dust cloud lingers

Exposure to asbestos fibres is to blame for most (>80%) cases of the notoriously incurable cancer, malignant mesothelioma. The UK death toll from asbestos-related mesothelioma is now reaching its peak, according to figures released by the Health and Safety Executive. In 2017, there were 2523 deaths from mesothelioma in the UK—almost double the 1317 deaths recorded in 1995. What are the reasons behind this surge?

In the 20th century, asbestos was used widely in the manufacture of fireproofing, insulation, and roofing materials. However, by the 1970s, it was linked to alarmingly high mesothelioma rates, especially in shipyard, factory, and construction workers. Consequently, the most dangerous forms of asbestos (blue and brown) were banned in the UK in 1985, and white asbestos was eventually barred in 1999. The long lag-time between asbestos exposure and mesothelioma development (around 20–50 years) means that the current UK peaks in mesothelioma deaths are probably a result of industrial exposure in the 20th century. However, numbers of diagnoses and deaths in the UK have begun to plateau in the past 5 years, and are predicted to decline in the coming years due to the effects of the legislation implemented several decades ago.

By contrast, in the USA, ten states and Washington, DC, are suing the Environmental Protection Agency for failing to enforce strict rules on the use of asbestos. An initial ban on asbestos in 1989 was overturned in 1991, and federal law still allows some regulated use of asbestos (eg, in roofing, ceiling, and flooring materials). Around 3000 new mesothelioma cases and 2500 related deaths are recorded annually in the USA, with the highest incidence in states with a history of shipbuilding and industry, such as Maine and Alaska.

The USA is not the only country that still uses asbestos. Although it is banned in 55 countries worldwide, many continue to mine and use it, with Russia and China among the top producers. In such nations, it still poses very real health risks. We can only expect the incidence of asbestos-related mesothelioma and other diseases in these countries to continue to rise unless governments act to address this highly preventable cause of premature death. ■ *The Lancet Oncology*

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For more on the **HSE report on mesothelioma rates and deaths in the UK** see https://www.theguardian.com/society/2019/jul/07/britains-death-toll-from-asbestos-at-crisis-level-figures-reveal

For more on the **lawsuit against the EPA** see https://www.medscape.com/viewarticle/915099

For more on the **initial asbestos ban in the USA** see https://theecologist.org/2018/dec/13/why-hasnt-us-banned-asbestos

For more on **mesothelioma incidence in the USA** see https://www.cancer.net/cancer-types/mesothelioma/statistics

For more on **mesothelioma deaths in the USA** see https://www.asbestos.com/mesothelioma/death-rate/

Are results from clinical trials reliable?

In this issue of *The Lancet Oncology*, Joseph C Del Paggio and Ian F Tannock report findings from an analysis of the fragility index in phase 3 randomised controlled trials (RCTs) used to support US FDA approvals of cancer drugs between 2014 and 2018. Nine of 17 trials assessed had a fragility index of 2 or less; if two patients or fewer in the experimental group had had a progression or overall survival event instead of no event, the results would not have been significant. Of the 17 approved drugs, only one had more than one phase 3 trial as supportive evidence. These results highlight a worrisome potential weakness in the evidence used by the FDA for approvals and beg the question: should more than one significant, positive phase 3 RCT be mandated for cancer drug approvals?

Arguments against requiring significant, positive results from multiple phase 3 RCTs are substantive (avoiding research waste), ethical (ensuring patients receive the likely superior drug), practical (survival endpoints have long follow-up, patient accrual is challenging, and high costs), and cynical (sponsors might be resistant to funding more than one trial). These arguments ignore the crucial point of Del Paggio and Tannock's analysis—that a second positive result is not a foregone conclusion. If the quantity of evidence required for drug approval does not change, we should demand real-world effectiveness (and not just toxicity) data for all approved drugs, either from phase 4 post-marketing trials or through real-world data from patients, and act on these results if they differ substantially from those originally submitted as evidence.

FDA decisions are based on extensive evidence from a broad range of studies, not just phase 3 RCTs. But the fragility index could serve as a useful marker of how much weight to give to phase 3 trial results. The addition of the fragility index to more traditional statistical approaches also challenges our ideas about clinical trial design, including statistical design, and whether we must redefine our notion of a positive result. A critical evaluation of these issues is warranted. ■ *The Lancet Oncology*

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For the **study by Del Paggio and Tannock** see **Articles** *Lancet Oncol* 2019; **20:** 1065–69