Appendix

*A note about the interventions*

The interventions considered here are known as “representative” interventions.[1](#_ENREF_1) They are mathematically equivalent to re-assigning each person-year with exposure above the binary cutoff to an exposure below the binary cutoff at random according to the observed distribution of exposures below the binary cutoff.

*G-estimation details and confidence intervals*

The analysis was based on the following structural accelerated failure time model:

(1)

where is observed survival time, is observed exposure at time , is the counterfactual survival time if never exposed, and is the unknown coefficient to be estimated.[2](#_ENREF_2),[3](#_ENREF_3) G-estimation of was achieved by solving an estimating equation (see Hernán et al, 2005[2](#_ENREF_2)) using a binary grid search within the search interval -0.9 to 0.9, a range that included all plausible (and many implausible) values for the coefficient.

For some bootstrap samples, g-estimation failed to produce an estimate within that interval. For example, this could happen when too few cases who had ever (or never) been exposed above the cutoff were selected into the sample. For each cutoff where at least one bootstrap sample (but fewer than 5% of them) failed to produce an estimate, the minimum and maximum estimates were reported instead of the 2.5th and 97.5th percentiles, yielding a conservative confidence interval. For straight fluids, this occurred for cutoff 0.1mg/m3 while for soluble fluids, this occurred for all cutoffs greater than or equal to 0.15mg/m3. For synthetic fluids, this occurred for every cutoff except 0, so nearly all confidence intervals are conservative. In addition, for one cutoff (0.05mg/m3 for synthetic fluids), eleven bootstrap samples failed, which is more than 5% of the samples. No confidence interval is reported for that estimate (which is, in any case, close to the null).

*Effect measure estimated*

The coefficient represents the log of the ratio of the median survival time that would have been observed if all workers had been exposed for the entire duration of follow-up to the median survival time if all workers had never been exposed. However, this interpretation is not very meaningful in our application: the autoworkers cohort includes follow-up after the end of employment, when exposure can no longer occur, thus making “always exposed” a problematic concept. We reported estimates for a different effect measure derived from the same coefficient: the sum over all COPD deaths of the difference , where is calculated for each person from the accelerated failure time model (equation (1)) using the g-estimate of .

Since the autoworkers cohort was not followed until all workers had died, administrative censoring would cause bias in the absence of proper adjustment, because survival to the administrative end of follow-up may depend on exposure. We adjusted by artificially censoring those workers whose COPD death would have been unobserved under at least one possible exposure scenario, as described in the references.[2](#_ENREF_2),[3](#_ENREF_3) Thus, under the assumptions described in the Discussion, our g-estimates of are unbiased. For each analysis, we then used the g-estimate to calculate the estimated total number of years of life saved among all individuals whose deaths from COPD were observed during the study period, including those artificially censored in the g-estimation step (even though some of those saved life years were after the administrative end of follow-up). Those who were administratively censored (that is, who were still alive at the end of follow-up) were not included in this sum. Different workers may have been artificially censored in the analyses of different cutoffs. Including the artificially censored cases was therefore necessary in order to obtain comparable estimates for different cutoffs, since our sums must refer to the same population for all cutoffs.

*Censoring weights*

We adjusted for loss to follow-up (<4%) and censoring by death from competing risks (<24%) using inverse probability of censoring weights.[2](#_ENREF_2) We used stabilized weights equal to the predicted marginal probability of remaining uncensored divided by the predicted conditional probability of remaining uncensored. The conditional probability of being uncensored at each time was obtained from a pooled logistic model using the following predictors: race, sex, current age and age at baseline (both linear), plant, an indicator for the year being before 1970 (when exposures were dramatically reduced), both current and previous exposures to all three fluid types as described in the text for the model predicting exposure, and intermittent time off work. The weights were moderate (range: 0.88 to 1.45) and did not require truncation.

Our use of inverse probability weighting to adjust for competing risks gives our results a somewhat odd interpretation: we estimate the impacts of interventions as if it were impossible to die from causes other than COPD. This scenario is unrealistic, but it is the only way to avoid assuming that death from competing risks is uninformative. However, a sensitivity analysis without adjustment for competing risks yielded similar, but consistently higher, estimates.

1. Taubman SL, Robins JM, Mittleman MA, Hernan MA. Alternative approaches to estimating the effects of hypothetical interventions. Alexandria, VA: American Statistical Association; 2008.

2. Hernan MA, Cole SR, Margolick J, Cohen M, Robins JM. Structural accelerated failure time models for survival analysis in studies with time-varying treatments. Pharmacoepidemiol Drug Saf 2005;14:477-91.

3. Chevrier J, Picciotto S, Eisen EA. A comparison of standard methods with g-estimation of accelerated failure-time models to address the healthy-worker survivor effect: application in a cohort of autoworkers exposed to metalworking fluids. Epidemiology 2012;23:212-9.