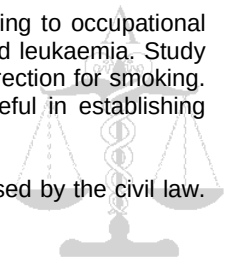
IIAC November 2010
IIAC Commissioned Reviews 2010: Cancer risk in Painters

IIAC observe a small increase in risk of lung cancer and bladder cancer in occupational painters. In their own analysis of the data, IIAC find the relative risk was approximately 1.25 and 1.10 respectively, each with high precision and statistically significant. However there was no correction for smoking. Other, work, reported since the IIAC review suggests an argument for material contribution could be attempted.

The purpose of review was to carry out "a systematic review of the evidence relating to occupational cancers in commercial painters". The focus was on lung cancer, bladder cancer and leukaemia. Study dates ranged from 1980 to 2009. Very few of the longitudinal studies made any correction for smoking. Case control studies often made a correction for smoking but are much less useful in establishing causation.



We have taken the opportunity to rehearse some of the arguments that would be used by the civil law. These provide a contrast with the arguments used by IIAC.

Q. are there circumstances in which the risks of cancer were more than doubled in commercial painters relative to a suitable comparator population?

In considering this question it should be noted that exposures via inhalation, skin contact and ingestion would include a wide variety of solvents, pigments, smoke and dusts many of which would appear on lists of actual or possible carcinogens. According to IIAC outright occupational causation would be supported by an observation of risk being at least doubled. IIAC has so far been spared from addressing the 'made worse' or 'made more likely' type of question; the related State compensation system can only operate at a higher level of certainty. The civil courts must deal with broader questions.

For there to be a material contribution there would need to be some understanding of mechanism e.g. several sources of a known carcinogen or, carcinogens which act via the same mechanism. In other words, the actual disease process and not just the risk of harm, must be in some way added to. The claimant must establish that the alleged breach would result in this nudge to the disease process.

Was it a big enough nudge? The total risk where people are exposed to the alleged hazard must be at least distinguishable from the total risk presented by other exposures and spontaneous disease. This must be established at a generic level and in light of the facts of a given case.

In properly designed studies the relative risk measures the effect of exposure to hazard, but only if all confounding factors and effect modifiers are accurately accounted for and the right comparator group is selected. For IIAC the comparator group would usually be the general population, for the civil law the choice of group would be influenced by the nature of any duty of care. The comparator group should represent those for whom the duty had been performed to the right standard. This could be a group for whom there was no exposure (all exposure was unreasonable), or a group for whom there was a reasonable exposure, it depends on the situation.

If the study design and execution is good enough, then the question of whether the overall risk at a given level of exposure is distinguishable from background comes down to statistics. Using the balance of probabilities principle from the civil law, the test would be whether or not a given measurement of total risk would be more likely than not higher than a given measurement of 'background' risk. This can be evaluated using single high quality studies or from collating the observations of multiple studies. It cannot be assessed without knowing the precision of any given measurement. The more precise a measurement the more confident you can be that two measured values (i.e. total risk and background risk) really are different. If the probability of two measurements being different is below 50% then the two measurements are in effect the same. There is no observable increase in risk.

As a final check, or in the absence of direct measurement, the effect of the exposure in question can be compared with the effect predicted from a dose-response relationship, usually measured at high levels of exposure and extrapolated to lower levels. Once again, the likelihood of a material contribution depends on whether the total risk at a given level of exposure can be distinguished from that of background risk. The precision of both risk estimates will be crucial to that assessment.

In case of lung cancer and bladder cancer smoking is the main confounding factor. Much of the opinion on distinguishable additional risk would be guided by the degree to which it was felt that smoking had been accurately accounted for.

So, for material contribution:

- There should be a mechanism[1] which means any non-occupational risk is directly increased by occupational risk.
- The effect of that specific contribution must be such that the total risk, including occupational risk, is, or is predicted to be, clearly different from and higher than the non-occupational risk. As a rule of thumb this would often occur when the total risk was just over one standard deviation higher than the background risk (assuming both were measured with same precision).

Given the diversity of exposures experienced by painters it would almost always be possible to show that something in the mix was the same as, or acted in the same way as tobacco smoke. For a causation argument to be sound, it would not be sufficient to show that total occupational risk was clearly greater than background risk; the risk must be attributable to the identified mechanisms, or if a less severe test is applied, 'Modes of Action'. If there is only one component at work which could cause cancer then it would be easier to show material contribution.

IIAC simplify these arguments by choosing a doubled risk test, based on occupation, rather than specific exposure at work. But this too is a simplistic test; it needs to include a statement about precision before it has a robust meaning. IIAC rely on the experience of its panel to decide if RR>2.0 has any meaning. Much of this experience is in relation to the practice and reliability of epidemiology. Some IIAC members are epidemiologists.

Epidemiologists, aware that the reported measurement precision often flatters the real precision of an experiment, argue that only when a reported difference is of at least 2 standard deviations do they consider the difference to be potentially real. At 2 standard deviations, there is a good chance that the background risk would be measured as being below the total risk experienced by painters (but study design should be carefully assessed in each case). Epidemiologists refer to their test as the 95% confidence interval.

Relative Risk estimates (e.g. occupational risk where duty is broken compared with occupational risk where duty is complied with) are often corrected for confounding factors and effect modifiers. If after correction the relative risk is still more than 2 standard deviations above 1.0, epidemiologists regard this as evidence of a real risk factor.

Key findings of this review into occupational painting:

a. For lung cancer there was evidence of an increased risk in the cohort and nested case control studies (summary unadjusted RR (95%CI) 1.25 (1.18 to 1.32) and also from the case control studies (1.28 (1.13 to 1.45)).

b. For bladder cancer there was evidence of an increased risk in the cohort and nested case control studies (summary unadjusted RR (95%CI) 1.10 (1.06 to 1.15) and also from the case control studies (1.37 (1.23 to 1.52)).

c. For leukaemia there was no evidence of an increased risk in the cohort and nested case control studies (summary RR (95%CI) 0.92 (0.79 to 1.07). The evidence from case control studies was deemed insufficient for conclusions to be drawn.

Comment
The risk estimates presented here were simply based on the ratio of observed to expected cases. Given the large numbers (several studies were combined into one analysis), the reported precision is high; the numbers such as they are should be reliable.

In none of the cancers considered here, was there a doubling of risk associated with working as a painter. It is unlikely there will be prescription for industrial injuries disablement benefit.

Cohort studies individually found small risk for lung cancer and bladder cancer, but were not corrected for smoking.

There was no dose response effect.

For civil cases the problem then moves on to one of material contribution rather than an outright presumption of causation.

[1] There is a current fashion for relaxing the mechanism test. In its place, 'Mode of Action' is emerging as the test of contribution. If benzene was common to both guilty and innocent exposures then mechanism of action would not be controversial. If benzene was the occupational carcinogen and a chemical which metabolised to benzene was the innocent exposure, mechanism would rarely be in dispute. Benzene and any other carcinogen would satisfy a Mode of Action test if both exposures led to for example, DNA damage of any kind.

Arguments in favour of material contribution: the risk is clearly greater than the background risk by more than 2 standard deviations, assuming there has been no bias. Given that the risk estimates for cohort studies (with no correction for smoking) and case control studies (corrected for smoking) were very similar, it could be said that smoking was not a factor in lung cancer and bladder cancer cases. And, painters are almost certainly exposed to carcinogens of some sort at work.

Arguments against: the reported cohort risk factors are unadjusted so may become insignificant if adjusted for known risk factors e.g. education level, smoking etc. Correction for smoking is absolutely vital if there is to be any confidence in a statistical association. The similarity of cohort and case control risk estimates could be luck. No evidence yet of any dose response effect (where tested, no dose-response pattern was observed).

Overall, although plausible that painting should increase the risk of lung and bladder cancer (since carcinogens are present), the evidence reported here does not provide a reliable basis for deciding there could be a material contribution. If relative risk in a fully adjusted model is different from background by more than 2 standard deviations and if a dose response effect is observed in cohort studies then material contribution would be more likely. Even so, the precision of a risk estimate would still be influential.

An analysis reported in 2010 (database 10#5-6 7 and 8) adds weight to a proposed dose response effect; dose measured by years of occupation.