*Question 1: We would be interested in HSE's view of the 2010 assessment of the Risks of environmental and occupational exposure to asbestos by the Health Council of the Netherlands.*

## Summary

Focus on a small selection of epidemiological studies that meet quality criteria relating to exposure assessment in an analysis by the Gezondheidsraad (GR) – the Health Council of the Netherlands – does not necessarily provide a better description of mesothelioma and lung cancer risk in relation to asbestos exposure for the purposes of general risk estimation than earlier meta-analyses based on a wider set of studies, such that by Hodgson and Darnton recently considered by WATCH. The underlying justification for the Dutch approach that an association between better study quality and increasing lung cancer risk is entirely due to an underestimation of exposure-response relationships in studies with lower quality exposure estimation may not necessarily be true. Other factors could explain why particular higher quality studies also show higher lung cancer risks than lower quality studies. A need to rely on lower quality studies to derive mesothelioma risks in relation to amphibole exposure shows that focussing only on higher quality studies does not yield estimates appropriate for the purpose of general risk assessment for mesothelioma, and further highlights that this may also be the case for lung cancer.

The GR approach found no consistency in lung cancer estimates among the four studies that met quality criteria (see Table 1).

**Table 1 Summary of studies used by GR for Lung Cancer**

| **Study** | **Industrial context / asbestos type** | **100 x $K_L$** | **95% CI** |
|---|---|---|---|
| South Carolina | Textile production / chrysotile | 2.97 | 2.12-3.83 |
| Libby miners* | Mining / Libby amphiboles | 0.88 | 0.36-1.40 |
| Rochdale | Textile production / chrysotile, some crocidolite | 0.52 | 0.21-0.82 |
| Swedish population* | Population based case-control study / Mixed exposures | 20.98 | 9.39-32.6 |
| **Summary** | **All above** | **1.64** | **0.34-2.95** |

**Not included in the original H&D analysis. The Libby miners were subsequently considered as part of the review by WATCH.*

Only one study (Rochdale) had a $K_L$ value within the 95% confidence interval of another study. Among these studies the highest $K_L$ value (20.98) is approximately 40 times higher than the lowest value (0.52). No attempt made to distinguish between types of asbestos for lung cancer and a single summary estimate of 100.$K_L$ = 1.64 (95% CI: 0.34-2.95) was derived for all fibre types.

Mesothelioma risk assessments were hampered by the lack of studies meeting the quality criteria (see table 2) and two other studies were used to derive the mesothelioma risk in relation to amphibole exposure.

**Table 2 Summary of studies used by GR for mesothelioma**

| **Study** | **Asbestos type** | **$K_M$** | **Used as summary value for:** |
|---|---|---|---|
| South Carolina | Textile production / chrysotile | $0.15 \times 10^{-8}$ | Chrysotile |
| Rochdale | Textile production / mixed: chrysotile, some crocidolite | $1.3 \times 10^{-8}$ | Mixed: chrysotile with up to 20% amphibole |
| Wittenoom miners* | Mining / crocidolite | $12 \times 10^{-8}$ | Pure amphibole (Combined summary= $8.0 \times 10^{-8}$) |
| New Jersey* | Insulation product manufacture/ amosite | $3.9 \times 10^{-8}$ | |

**Did not meet quality criteria*

The combined summary $K_M$ value based on the two amphibole cohorts – neither of which met quality criteria – is a factor of about 50 higher than that used as a summary estimate for chrysotile exposure, based solely on the South Carolina study in which there were 3 actual mesothelioma deaths.

The reliance on so few studies in the GR approach for both lung cancer and mesothelioma makes the resulting estimates vulnerable to bias because of the influence of particular studies. The South Carolina study is particularly influential in the GR analysis; this study has been the subject of extensive debate and its estimates have been regarded, at least by some, as an outlier in the overall set of values.

The Hodgson and Darnton (H&D) analysis recently considered by WATCH covers a larger number of studies. While there are many sources of limitations in all studies, there is a degree of consistency in the estimates for mesothelioma and lung cancer once fibre type differences are taken into account. This was further corroborated by evidence (also considered by WATCH) from additional studies since the original publication (which also fall short of GR quality criteria). The consistency of these estimates led WATCH to conclude that "…for different fibre types and different exposure levels within, and reasonably close to, the exposure range within which observational data are available, the H&D model appears generally robust and can be used to differentiate between the relative magnitudes of risk."[i]

[i] HSE 2011. Final WATCH position on asbestos risk assessment: February 2011. Available at: www.hse.gov.uk/aboutus/meetings/iacs/acts/watch/240211/asbestos-final%20position-statement.pdf

**Background**

The Gezondheidsraad (GR) – the Health Council of the Netherlands – recently published an updated meta-analysis of available epidemiological data to estimate the risk of mesothelioma and lung cancer per unit exposure of asbestos[1] and Lenters and coworkers also published a related meta-analysis of lung cancer in relation to asbestos exposure with specific focus on the impact of study quality on risk estimates[2]. The source data potentially in scope for analysis (i.e. various historic epidemiological studies of asbestos exposed workers) is broadly the same as that used in the Hodgson and Darnton (H&D) 2000[3] meta-analysis considered in detail by the WATCH committee in the UK, and other meta-analyses, such as that by Berman and Crump (B&C) carried out for the Environmental Protection Agency in the US[4,5]. The aim of all of these analyses is to draw out the best picture of the risk of mesothelioma and lung cancer per unit exposure from available data for the purpose of risk assessment in general settings.

A key element of the GR analyses is the way in which the impact of study quality – particularly in relation to exposure measurement in the contributing epidemiological studies – was taken into account. The approach adopted in the final GR assessment was to derive summary risk estimates from the small subset of available studies which met certain quality criteria. This differs from the approach adopted by Berman and Crump who included all studies with sufficient data to implement their methodological approach, and then took account of additional variability introduced due to limitations in methodology or study quality. The original H&D analysis did not take account of study quality directly, though it did consider potential reasons for inconsistency in risks estimates and the implications for the development of summary measures for use in general risk assessment. The impact of study quality and the dependence of the H&D risk models on the results of certain studies was considered as part of the recent review by WATCH[6].

It is also important to note at the outset that the GR study was commissioned specifically for developing occupational and environmental exposure standards intended to control risk to specified level. The review by WATCH in the UK was more open ended and focussed on what can be said with confidence about the risks at different exposure levels in order to provide a steer to those that may wish to estimate risks arising from specific asbestos exposure scenarios. The regulatory regime in the UK does not regard control limits as defining an acceptable level of risk to workers. Instead they are part of a framework for ensuring the exposures are reduced as low as reasonably practicable.

## Comparison of GR and H&D analyses

*Lung cancer*

In the GR analysis, the lung cancer risk estimate ($K_L$) is the slope value in the linear regression model, $RR=1+K_L.X$, where RR is the relative risk and X is the cumulative asbestos exposure in f/ml.yrs. Expressed as $100xK_L$, this is then equivalent to the summary measure of $R_L$ (the percent excess lung cancer risk per f/ml.yr) calculated in H&D based on the overall lung cancer morality and overall average cohort exposure (rather than within cohort regressions).

The GR summary estimate was $100.K_L = 1.64$ (95% CI: 0.34-2.95), meaning that a cumulative exposure of 100 f/ml.yr will cause an excess risk of 1.64, or a relative risk of 2.64. No distinction was made between asbestos fibre types: the authors concluded that when analysis of lung cancer risk is restricted to good quality studies, "the epidemiological evidence base is too sparse to draw deductions about potency differences per fibre type". This will be clear when considering the small set of four studies on which the final GR summary value is based (see Table 1).

H&D produced separate summary risk estimates for chrysotile and amphibole asbestos on the basis that a clear pattern of risk is evident for these categories once certain features of the overall dataset are taken into account. This led to summary values of $R_L$=0.1 for commercial chrysotile and $R_L$=5 for pure amphibole exposure.

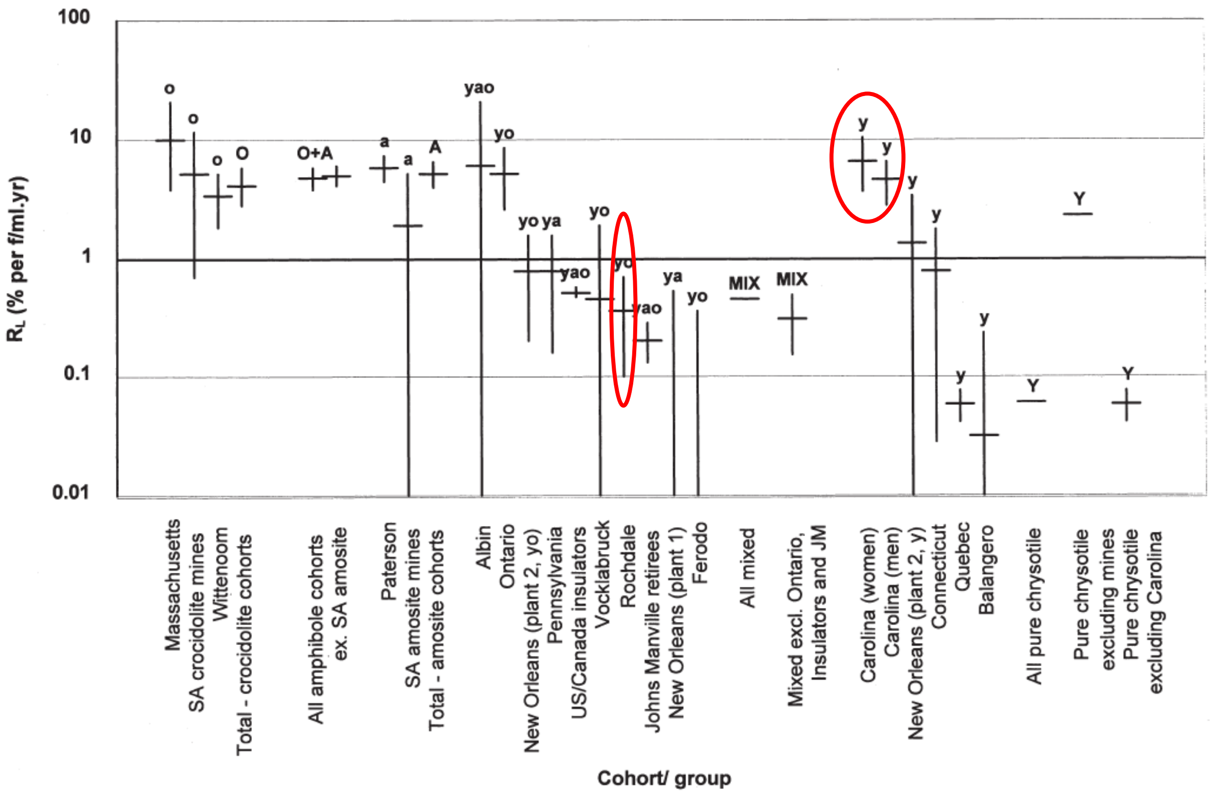
The H&D risk estimate of $R_L$=5 is derived from five available amphibole cohorts, none of which meet the quality criteria for inclusion in the GR analysis. The individual $R_L$ values for these studies are reasonably consistent, ranging from 2-10 with a mean of about 5.

A much lower value of $R_L$=0.1 for commercial chrysotile was suggested by arguing that:

1. after discounting the South Carolina cohort there is a fairly clear pattern of risk by asbestos fibre type: pure amphibole cohorts show the highest risks per unit exposure, chrysotile cohorts the lowest, and mixed fibre exposure cohorts an intermediate risk level;
2. the South Carolina value looks untypically high compared with other pure chrysotile cohorts, and is therefore best considered separately: estimates for remaining chrysotile cohorts are reasonably consistent statistically at a much lower level;
3. the pure chrysotile risk estimate should be lower than the average for mixed exposure cohorts of about 0.5, but probably higher than that for the Quebec miners cohort estimate of 0.06 (since processing of asbestos appears to confer additional risk than mining alone).

$R_L$ values for the wider set of cohorts considered by H&D are shown in Figure 1 below which is a reproduction of Figure 3 from the original paper. Two of studies considered by GR were not included: the Libby miners cohort and the Swedish population case-control study. The other two studies considered by GR are highlighted in red.

**Figure 1: Exposure-specific excess lung cancer mortality ($R_L$) by cohort and fibre type groupings with 95% confidence intervals (not shown for groups with very significant heterogeneity)**




*Key: o=crocidolite, a=amosite, y=chrysotile; mixed fibre cohorts shown by relevant combination of symbols; various summary values for cohort groupings shown in capitals.*

*Mesothelioma*

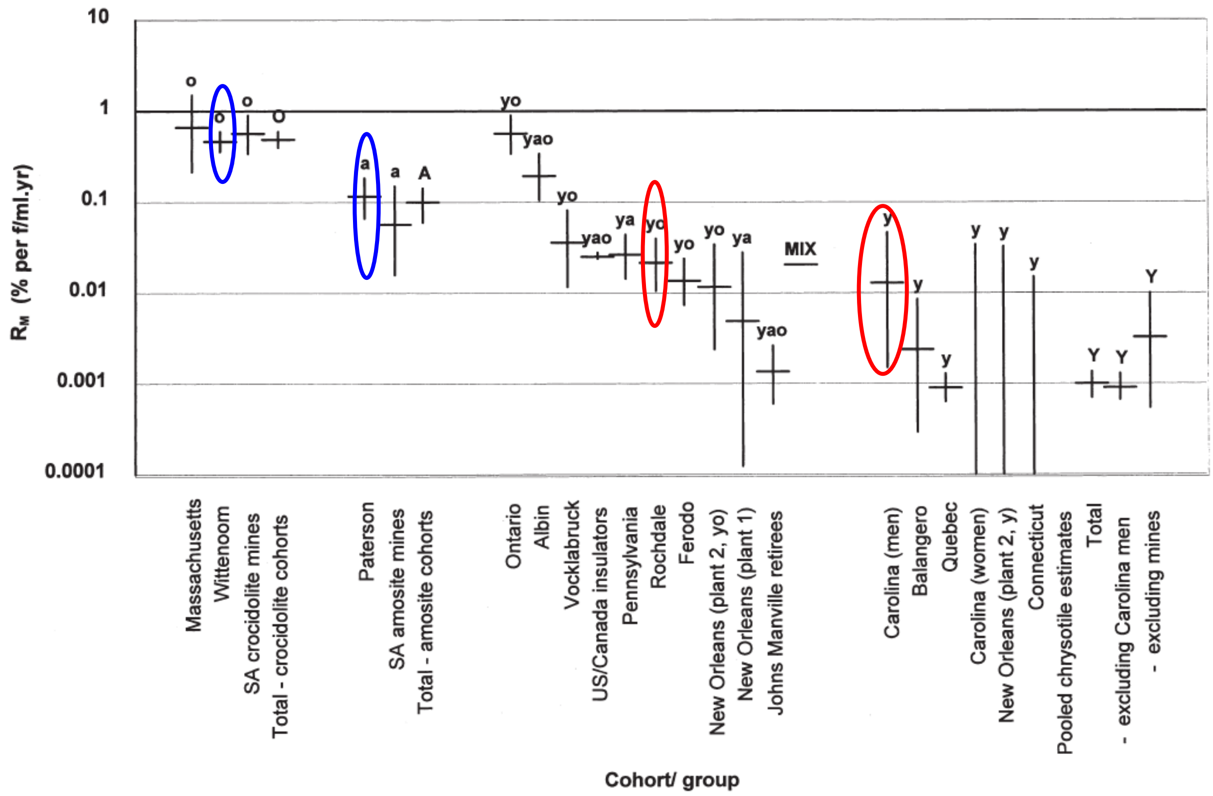
As for lung cancer, the methodological approaches for assessing mesothelioma risk are different in the GR and H&D studies: again the former used within-cohort regressions (derived by Berman and Crump) and the latter used cohort-level summaries of risk and average exposure. Both analyses result in summary risk estimates for each cohort ($K_M$ for GR; $R_M$ for H&D) which are then combined in meta-analyses to derive overall summary risk estimates for each asbestos fibre type.

Only two of the cohorts that met the GR quality criteria had sufficient data to derive estimates of $K_M$: the South Carolina textiles cohort ($0.15x10^{-8}$) and the Rochdale textiles cohort ($1.3x10^{-8}$), see Table 2. These values are taken as summary estimates for pure chrysotile and mixed chrysotile/amphibole exposure respectively. Because the GR required an amphibole risk estimate, a summary value ($8.0x10^{-8}$) was derived from the two available amphibole cohorts with sufficient data – the Australian crocidolite miners ($12x10^{-8}$), and New Jersey amosite factory workers, ($3.9x10^{-8}$) – although these did not meet quality criteria. The ratio of risk per unit exposure for chrysotile to amphibole based on these values is therefore approximately 1:50, the chrysotile value being determined entirely by the South Carolina cohort. (Note, that exposure estimates for the New Jersey site were derived long after it closed down and moved to Tyler, Texas; the exposures at Tyler were measured shortly before it was closed. Similarly, measurements for the Australian mine at Wittenoom were taken a few weeks before it shut down.)

The H&D analysis derived separate summary risk estimates for the two amphibole types based on three crocidolite cohorts (combined $R_M$=0.5) and two amosite cohorts ($R_M$=0.1) given consistency between risk estimates for studies within these categories. A much lower estimate of $R_M$=0.001 was derived from the chrysotile cohorts, strongly influenced by the Quebec miners study (which contributed 33 of the 37 mesothelioma deaths that occurred across all six chrysotile cohorts). The ratio of risk per unit exposure for chrysotile to amosite to crocidolite is thus 1:100:500. The $R_M$ value for South Carolina was more than 10 times higher than that for Quebec but carried little weight being based on only 2 deaths (3 in the subsequent update by Hein *et al.*). This largely accounts for the difference in the chrysotile to amphibole risk ratio between the GR and H&D analyses.

$R_M$ values for the wider set of cohorts considered by H&D are shown in Figure 2 below which is a reproduction of Figure 2 from the original paper. The studies considered by GR are highlighted (in red for those meeting quality criteria and blue otherwise).

**Figure 2: Exposure-specific mesothelioma mortality ($R_M$) by cohort and fibre type groupings with 95% confidence intervals (not shown for groups with very significant heterogeneity)**




*Key: o=crocidolite, a=amosite, y=chrysotile; mixed fibre cohorts shown by relevant combination of symbols; various summary values for cohort groupings shown in capitals.*

## Discussion

The differences in the conclusions of the GR and H&D analyses can be summarised as follows. For lung cancer, application of quality criteria means that pure amphibole cohorts are largely discounted in the GR analysis which is then influenced strongly by the South Carolina textile cohort. In contrast, the H&D analysis treats the South Carolina cohort as a special case which is likely to describe the risk only in the specific circumstances of textile manufacture. Drawing on the remaining set of cohorts, H&D then found a substantial difference between the lung cancer risk due to amphibole and chrysotile. For mesothelioma, application of quality criteria leads to the GR chrysotile risk summary being based entirely on the South Carolina cohort, whereas the estimate in the H&D analysis is strongly influenced by the substantially lower value from the Quebec study. GR produced a combined mesothelioma estimate for amphibole, whereas H&D produced separate estimates for amosite and crocidolite.

An important motivating factor in the GR analysis was the observation that higher quality studies tend to give higher lung cancer risks per unit exposure. This has been interpreted as being due to the substantial uncertainties in the estimation and assignment of asbestos exposure leading to an attenuation of the slope of dose response relationships in some studies, and that this classical bias towards the null then resulted in an underestimation of the risk per unit exposure in meta-analyses. However, in the context of the relatively small number of available studies which differ in various respects, it is not clear that the presence of an association between increasing lung cancer risk and study quality is attributable to differences in the quality of exposure assessment or to other factors that vary between studies. The subset of studies on which the final GR summary estimate is based is restricted to just four studies which come different industrial settings and with individual risk estimates that are not statistically consistent with each other. This tends to undermine the argument that restricting attention to high quality studies yields a more consistent picture.

The relatively high risk estimate from the South Carolina study has a large influence on the GR lung cancer summary risk value. This study has been the subject of extensive debate, and although it is of high quality, it is not clear that the risk estimate is appropriate for general risk estimation purposes. The question of whether risk estimate is high because this is a good quality study which gives a good view of the true risk that applies in general, or whether the study gives a good view of the risk in this particular context, but isn’t generalisable because of other factors (such as the preponderance of long thin fibres in exposures in this setting) still remains.

In contrast to the analysis of lung cancer, an association between increasing risk and study quality is not evident for mesothelioma. Although the South Carolina cohort does suggest a higher mesothelioma risk per unit exposure than the other chrysotile cohorts, this is still very substantially lower than the risk observed in amphibole cohorts which do not meet the GR quality criteria. In the GR analysis it was thus necessary draw on evidence about mesothelioma risk in relation to amphiboles from lower quality studies. The implication is that these studies, although deficient, provide overwhelming evidence about a higher risk associated with amphibole exposures and so it would not be appropriate to use a single risk estimate based only on those studies that met the quality criteria. This raises further doubt about whether the association seen for lung cancer can be attributed to the quality of the exposure assessment rather than other factors.

The GR risks estimate for mesothelioma in relation to chrysotile is based solely on the South Carolina study. While the higher risk seen in this cohort may be applicable to chrysotile exposure in that particularly industrial setting (though it is highly uncertain being based on only 3 cases), again it is not clear that it provides a sound basis for risk estimation in general settings.

In summary, while the GR analyses do demonstrate a relationship between increasing study quality and increasing lung cancer risk, restricting attention to a small number of studies that meet quality criteria does not necessary provide a better view of the risk per unit exposure for the purposes of general risk estimation than earlier meta-analyses.

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