Keith N. Cole
Vice President, Government Relations and
Environment, Health, and Safety

T +1 410.531.4709
Keith.Cole@grace.com

W. R. Grace & Co.-Conn.
7500 Grace Drive
Columbia, MD 21044

June 2, 2014

Dr. Kenneth Olden, Director
National Center for Environmental Assessment
U.S. Environmental Protection Agency
William Jefferson Clinton Building
1200 Pennsylvania Avenue, N.W.
Mail Code 8601P
Washington, D.C. 20460

RE: Important Scientific Information Related to Draft Libby Amphibole Asbestos (LAA) Toxicological Assessment

Dear Dr. Olden:

We understand that EPA has plans to continue working on the draft Libby Amphibole Asbestos (LAA) Toxicological Assessment through at least October, 2014. To aid EPA's ongoing work, we bring to your attention several important studies that have a significant bearing on EPA's deliberations regarding the non-cancer Reference Concentration (RfC) and the fundamental question of whether pleural plaques can serve as a scientifically supportable critical effect for deriving the RfC. We encourage you and your staff to discuss with the authors their findings and would be happy to facilitate such a discussion at your convenience.

As you know, under EPA policy a critical effect must be shown to be "likely to impair the performance or reduce the ability of an individual to function. . . ." The below-described literature, all conducted independently but with funding from W. R. Grace, strongly suggests that pleural plaques do not meet EPA's definition of a critical effect. A rigorous and complete systematic literature review and integration of the evidence regarding selection of the critical effect by EPA should include consideration of the scientific merits of these studies.

First, a peer-reviewed study published in the highly regarded medical journal *Chest*, May 8, 2014 (Clark *et al.*, 2014), evaluates pleural plaques and lung function in LAA-exposed Libby miners. This study of the highest LAA-exposed population uses the most accurate methods for diagnosis and classification of lung abnormalities – High Resolution Computed Tomography, or HRCT – and determines that LAA-induced pleural plaques did not cause decrements in lung function. A few points about this study:

- This study's findings are consistent with the larger trend found in the body of studies that rely upon HRCT. (See comments about the Kerper *et al.* study, below).

- This study's use of HRCT to identify abnormalities in the lungs eliminates the bias found in other studies (such as Weill *et al.*, 2011 and Larson *et al.*, 2012) from relying upon X-rays. It is well accepted in the medical community that X-ray radiography is prone to misdiagnosis of pleural plaques (*e.g.,* extrapleural fat can be mistakenly identified as plaques) and underdiagnosis of other lung abnormalities (*e.g.,* fibrosis) that affect lung function. In contrast, HRCT is more reliable because of its superior contrast sensitivity and cross-sectional imaging format.
- As another improvement over many of the prior studies, multiple pulmonary function test parameters are evaluated in this study – forced expiratory volume (FEV1), forced vital capacity (FVC), FEV1/FVC, total lung capacity (TLC), expiratory reserve volume (ERV), and residual volume (RV).
- This study finds that there were no statistically significant differences in lung function parameters between miners with pleural plaques alone and those with normal HRCT findings.

Here is a link to this study: http://journal.publications.chestnet.org/article.aspx?articleid=1868832.

Second, a peer-reviewed paper published in *Critical Reviews in Toxicology* (Moolgavkar *et al.*, 2014), concludes that "***the overall weight of evidence does not establish an independent adverse effect of pleural plaques on pulmonary function***." This paper evaluates whether pleural plaques are an adverse condition as defined by EPA based on a review of the literature that EPA relied upon in its Draft Assessment. It identifies the serious methodological limitations and inconsistent findings of these collective studies. The reviewed studies contained significant sources of confounding, including reliance on insensitive X-ray imaging (rather than HRCTs), failure to control for bias of those reading the X-rays, and significant inconsistency among the findings of the various papers when one tries to correlate the findings with the type of lung function measurement. This paper also identifies other scientific issues of concern in the Draft Assessment, such as that the data are too sparse to inform the exposure-response relationship in the low-exposure region critical for estimation of an RfC. Here is the link to this recent publication: http://informahealthcare.com/doi/abs/10.3109/10408444.2014.902423

A third study also assesses the effect of pleural plaques and the potential for bias due to reliance on X-ray imaging to diagnose pleural plaques. (Kerper, 2014, presented at the Society of Toxicology (SOT) 53rd Annual Meeting, Phoenix, AZ). This SOT presentation evaluates the literature that diagnoses pleural plaques by use of HRCT and concludes the following:
1) studies that rely upon less accurate X-rays and/or that combined pleural plaques with other lung abnormalities are not reliable indicators of pleural plaque effects on lung function; and
2) there is no reliable association between the presence of pleural plaques in asbestos-exposed populations and lung function deficits. While EPA staff likely already has this SOT presentation, we are enclosing it with this letter for your convenience.

Thorough consideration of these papers is critically important for helping to ensure that the LAA literature review is complete and unbiased. Indeed, the SAB Peer Review of the LAA Assessment recommended that EPA conduct a more detailed literature review on this very question of the selection of a critical effect. Moreover, these papers help to identify and address

bias and confounders in the literature. Identification of bias is a touchstone standard under the EPA's own Information Quality Act standards for scientific quality, as well as the National Academies' 2011 recommendation to identify the "potential for information bias" and the National Academies' 2014 statement that "assessment of risk of bias is a key element in systematic-review standards." (See the National Academies' 2011 "Roadmap for Revision" of the IRIS Program and its 2014 "Review of EPA's [IRIS] Process"). The above Clarke study is particularly important to consider because it avoids X-ray bias and uses a range of lung function measures. The Kerper paper identifies studies that use HRCT (avoiding X-ray bias) that neither the Draft Assessment nor the SAB Peer Review had previously considered. Furthermore, the Moolgavkar and Kerper papers are particularly useful because they help to identify bias in the scientific literature that the Draft Assessment relied upon. These studies aid precisely the type of evaluation needed in order to achieve a scientifically sound result. Furthermore, these studies affirm the importance of EPA implementing the National Academies' recommendations, including the importance of: a thorough literature review; publication of transparent evidence tables; identification of confounders and sources of information bias; and integration of the evidence.

In sum, these new scientific studies are directly relevant to the recent NAS recommendations for continued improvement in the IRIS program. We encourage you and your staff to discuss with these authors their findings. If we can facilitate this discussion, we would be happy to assist. We appreciate your continued time and attention to this issue.

Sincerely yours,

Keith N. Cole

cc: Vincent Cogliano, U.S. EPA
Lynn Flowers, U.S. EPA
David Bussard, U.S. EPA
Babasaheb R. Sonawane, U.S. EPA

Enclosures

Presented at 53rd Annual Meeting and ToxExpo
Society of Toxicology (2014)
Phoenix, AZ
March 23 - 27, 2014

Do Asbestos-Induced Pleural Plaques Cause Lung Function Deficits?

Laura Kerper, Ph.D.
Heather Lynch, M.P.H.
Lawrence C. Mohr, M.D.*
Julie Goodman, Ph.D., DABT

*Medical University of South Carolina

Abstract 1811, Poster 147

ABSTRACT

While there is general agreement that pleural plaques are biomarkers of asbestos exposure, there is debate in the scientific community over whether pleural plaques cause lung function deficits. Many of the studies that addressed this issue were subject to certain limitations. In most studies, pleural plaques were diagnosed by radiography, which is less accurate than high resolution computed tomography (HRCT) and can lead to misdiagnoses. Some studies reported lung function changes in subjects that had lung abnormalities in addition to pleural plaques, so that the contribution of pleural plaques to deficits was unknown. To eliminate these sources of uncertainty, we conducted the first comprehensive analysis of the associations between pleural plaques and lung function based on epidemiology studies in which 1) pleural plaques were diagnosed by HRCT and 2) individuals were identified with pleural plaques and no other lung abnormalities. We identified and analyzed 17 relevant studies. We looked for patterns within and across studies and examined whether associations were reproducible. Only three of the 17 studies reported statistically significant associations between pleural plaques and some measure of lung function. Among these three studies, the lung function parameters were not consistent, suggesting that the associations were not likely causal. In addition, mean asbestos exposures in all three studies were higher in the subjects with pleural plaques than in the subjects without. This suggests that, if the effects were not due to chance, the asbestos exposure itself, rather than pleural plaques, may have been responsible for observed lung function deficits. Taken as a whole, the direction of effect (*i.e.*, lung function deficit *vs.* improvement) varied among studies, indicating the absence of even subtle effects and that the lack of effect noted in the majority of studies was not a result of low statistical power. We conclude that there is no reliable association between the presence of pleural plaques in asbestos-exposed populations and lung function deficits.

OBJECTIVE

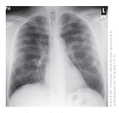
Review and analyze the studies with the most accurate methods for pleural plaque diagnosis and lung function measurement to determine whether they support the hypothesis that pleural plaques can affect lung function.

BACKGROUND

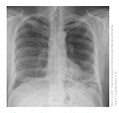
- Many studies have evaluated the effects of pleural plaques on lung function; the results of these studies are inconsistent.
- Variable methods were used in these studies to diagnose pleural plaques and measure lung function, which may have influenced the results.
- HRCT is a more accurate tool for diagnosis of lung abnormalities than X-ray radiography.
- Other lung abnormalities that may affect lung function include diffuse pleural thickening, emphysema, bronchiectasis, asbestosis, and other parenchymal fibrosis.

Figure 1 X-ray radiography *vs.* HRCT for identifying pleural plaques

X-ray radiography
Pleural plaques are difficult to distinguish, and other conditions (*e.g.*, diffuse pleural thickening, fibrosis) may not be apparent.

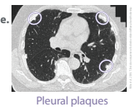


Pleural plaques

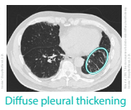


Diffuse pleural thickening

HRCT
Pleural plaques are easily distinguishable.



Pleural plaques



Diffuse pleural thickening

METHODS

We conducted a literature search with the PubMed search engine using the following terms:

pleural plaques and lung function

pleural plaques and asbestos

asbestos and lung function

We identified **64 studies:**

43 Employed X-ray radiography only; excluded from analysis.

4 Did not report lung function measurements in subjects with only pleural plaques; excluded from analysis.

17 Used HRCT to diagnose pleural plaques and included subjects with pleural plaques only; included in the analysis.

3/17 **Only three of the 17 studies reported statistically significant differences** in some (but not all) lung function measurements between subjects with and without pleural plaques. The lung function parameters with significant changes were not consistent across these three studies.

Hillerdal *et al.*, 1990
MVV ↓ MEF/FEF$_{50}$ ↓
No significant change in FEV$_1$, VC, TLC, FEV$_1$/VC, FEF$_{50}$

Rui *et al.*, 2004
FEV$_1$ ↓ VC ↓ TLC ↓
No significant change in FEV$_1$/VC

Clin *et al.*, 2011
FEV$_1$ ↓ FVC ↓ TLC ↓
No significant change in FEV$_1$/FVC, RV

All three reported greater asbestos exposure in the group with pleural plaques than the group without pleural plaques. If associations were not due to chance, asbestos exposure could be responsible for lung function effects.

RESULTS

Table 1 Summary of Changes in Lung Function in 17 Studies

Lung Function Parameter	Not Significant, Values Not Reported	Not Significant, No Change	Not Significant, Improvement	Not Significant, Deficit	Statistically Signficant Deficit
Forced expiratory volume in 1 second (FEV$_1$)	4		5	4	2
Forced vital capacity (FVC)	4		4	4	1
FEV$_1$/FVC	3	1	1	5	
Vital capacity (VC)			2	1	1
Total lung capacity (TLC)	4			2	2
Maximal voluntary ventilation (MVV)					1
Forced expiratory flow at the level when 50% of the FVC remains exhaled (MEF)	1		2	1	
MEF/Flow at 50% of FVC (FEF$_{50}$)					1
Maximal midexpiratory flow (MMEF)			1	2	
Residual volume (RV)	1			1	
Diffusing capacity for carbon monoxide (DL$_{co}$)	4		4	2	

Figure 2 Total Lung Function Measurements

21 Not Significant, Values Not Reported

1 Not Significant, No Change

19 Not Significant, Improvement

22 Not Significant, Deficit

Inconsistent direction in nonsignificant results

Lack of consistent direction of effect suggests nonsignificant results are not due to low statistical power.

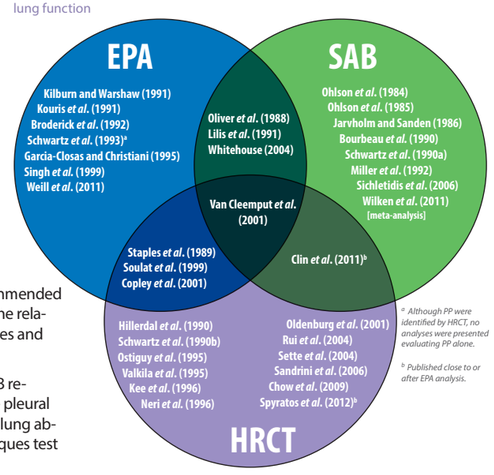
8 Statistically Significant Deficit

Lung function parameters with significant changes were not consistent

DISCUSSION

- In the 2011 draft *Toxicological Review of Libby Amphibole Asbestos*, EPA chose pleural plaques as the most sensitive adverse effect on which to base the Reference Concentration (RfC). The Science Advisory Board (SAB) agreed with this choice but also stated, "It is important to provide a more detailed review of the literature to support the use of LPT as the appropriate endpoint…"
- Among other things, SAB recommended review of studies that address the relationship between pleural plaques and lung function.
- Most of the studies EPA and SAB reviewed used X-rays to diagnose pleural plaques and/or included other lung abnormalities with the pleural plaques test group.
- EPA and the SAB did not consider several relevant studies using HRCT and therefore the evaluation of literature is incomplete.

Figure 3 Studies included in EPA, SAB, and HRCT study review of pleural plaques and lung function



a Although PP were identified by HRCT, no analyses were presented evaluating PP alone.

b Published close to or after EPA analysis.

CONCLUSION

- Studies that use X-ray radiography and/or combine pleural plaques with other lung abnormalities are not reliable indicators of pleural plaque effects on lung function.
- There is no reliable association between the presence of pleural plaques in asbestos-exposed populations and lung function deficits.

Acknowledgement

This study was funded in part by W.R. Grace & Co.

FULL CITATIONS AVAILABLE UPON REQUEST. IF YOU WOULD LIKE A REPRINT OF THIS POSTER, PLEASE LEAVE A BUSINESS CARD IN THE ENVELOPE.

Pleural Plaques Diagnosed by High Resolution Computed Tomography (HRCT) and Lung Function in Asbestos-Exposed Populations.

This table summarizes associations between pleural plaques and lung function in studies in which 1) HRCT was used to diagnose or confirm the presence of pleural plaques, and 2) individuals with pleural plaques did not have other diagnosed lung abnormalities.

Study	No. of Participants	No. with Pleural Plaques Only	Cohort	Location	Asbestos Exposure Measure	Avg. Estimated Exposure	Measure of Lung Function	Result (Mean ± SD)		*p* value
								Control	Pleural Plaques	
Staples *et al.*, 1989	76	NR	Asbestos workers	US	Duration (mean years)	No PP: 14.5 With PP: 20.8	Air flow	NR	NR	>0.05
							Lung restriction	NR	NR	
							DL_{CO}	NR	NR	
Hillerdal *et al.*, 1990	23	13	Hospital pulmonary patients with occupational asbestos exposure	Sweden	Duration (mean years)	No PP: 0 With PP: 15-29	FEV_1, %	NR	98 ± 10	>0.05
							VC, %	NR	97 ± 11	>0.05
							FEV_1/VC	NR	98 ± 7	>0.05
							TLC, %	NR	96 ± 8	>0.05
							MVV, %	**NR**	**91 ± 11**	**<0.05**
							FEF_{50}, %	NR	95 ± 22	>0.05
							MEF/FEF_{50}, %	**NR**	**118 ± 27**	**<0.05**
Schwartz *et al.*, 1990	16	9	Sheet metal workers	US	Duration (years)	No PP: 33.3 ± 6.6 With PP: 30.3 ± 7.2	FEV_1, %	110.4 ± 9.1	100.1 ± 17.2	>0.05
							FVC, %	104.9 ± 6.7	96.0 ± 11.8	
							FEV_1/FVC	76.1 ± 6.4	75.1 ± 7.9	
							TLC, %	121.9 ± 12.5	116.7 ± 13.9	
							RV, %	120.7 ± 21.9	121.6 ± 42.5	
							DL_{CO}, %	111.6 ± 23.2	111.8 ± 16.3	
Ostiguy *et al.*, 1995	247	54	Copper refinery workers	Canada	Duration (years)	No PP: 25.7 ± 0.5 With PP: 26.8 ± 1.0	FEV_1, %	111	107	>0.05
							FVC, %	106	104	
							MMEF, %	114	106	
Valkila *et al.*, 1995	59	23	Construction workers	Finland	Duration (mean years)	30	FEV_1, %	NR	NR	>0.05[a]
							FVC, %	NR	NR	
							DL_{CO}, %	NR	NR	
Kee *et al.*, 1996	106	44	Shipyard and construction workers	US	Duration (years)	26.5 ± 12	FEV_1/FVC	78 ± 7	74 ± 10	>0.05
							FVC, %	73 ± 19	78 ± 14	
							DL_{CO}, %	70 ± 23	88 ± 20	

Study	No. of Participants	No. with Pleural Plaques Only	Cohort	Location	Asbestos Exposure Measure	Avg. Estimated Exposure	Measure of Lung Function	Result (Mean ± SD)		*p* value
								Control	Pleural Plaques	
Neri *et al.*, 1996	119	50	Asbestos workers	Italy	Duration (years)	No PP: 4.8 ± 4.4 With PP: 9.1 ± 5.5	FEV_1	NR	NR	>0.05
							FVC	NR	NR	
							FEV_1/FVC	NR	NR	
							TLC	NR	NR	
							MEF_{25-75}	NR	NR	
							DLco	NR	NR	
Soulat *et al.*, 1999	170	84	Former insulation workers	France	Duration (years)	12.9 ± 0.6	FEV_1, %	108.4 ± 3.15	112.6 ± 2.40	>0.05
							FVC, %	108.9 ± 2.60	110.2 ± 2.03	
							MEF, %	111.1 ± 3.66	116.1 ± 2.96	
							MMEF, %	76.9 ± 4.53	81.1 ± 4.02	
Copley *et al.*, 2001	50	NR[a]	Patients with benign pleural disease	England	NR	NR	FEV_1	NR	NR	>0.05
							FVC	NR	NR	
							TLC	NR	NR	
							RV	NR	NR	
							Dco	NR	NR	
Oldenburg *et al.*, 2001	43	21	Asbestos workers	Germany	Duration (mean years)	30.7	FEV_1, %	86.58 ± 28.09	91.67 ± 20.25	>0.05
							FVC, %	89.89 ± 11.86	88.8 ± 13.89	
							FEV_1/FVC	94.9 ± 19.48	98.58 ± 13.48	
							MEF, %	93.07 ± 37.69	90.14 ± 36.79	
Van Cleemput *et al.*, 2001	73	51	Cement factory workers	Belgium	CEI	26.3 ± 12.6 f-years/ml	FEV_1, %	103.8 ± 13.7	104.1 ± 12.9	0.24
							VC, %	109.8 ± 14.9	110.5 ± 13.4	0.24
							FEV_1/VC	0.78 ± 0.07	0.78 ± 0.07	1.00
							PEF, %	108.7 ± 21.5	100.5 ± 23.3	0.48
							MEF, %	103.0 ± 35.7	109.2 ± 25.02	0.27
							TL_{CO}, %	97.2 ± 15.5	102.0 ± 16.5	0.93
Rui *et al.*, 2004	103	36	Asbestos workers	Italy	Duration (years)	No PP: 22 ± 6 With PP: 30 ± 6	FEV_1, %	**102 ± 13**	**95 ± 14**	**<0.05**
							VC, %	**96 ± 11**	**90 ± 10**	**<0.05**
							FEV_1/VC	78 ± 6	77 ± 7	>0.05
							TLC, %	**97 ± 9**	**91 ± 9**	**<0.05**
Sette *et al.*, 2004	82	NR	Cement workers	Brazil	Duration (years)	14.5 ± 10.1	Gas exchange	NR	NR	>0.05[a]

Study	No. of Participants	No. with Pleural Plaques Only	Cohort	Location	Asbestos Exposure Measure	Avg. Estimated Exposure	Measure of Lung Function	Result (Mean ± SD)		*p* value
								Control	Pleural Plaques	
Sandrini *et al.,* 2006	91	32	Patients with asbestos-related disorders	Australia	NR	NR	FEV_1, %	92 ± 16.9	93 ± 13.2	>0.05
							FVC, %	94 ± 13.5	95 ± 2.4	>0.05
Chow *et al*., 2009	86	26	Asbestos workers	Australia	NR	NR	FEV_1, %	91.65 ± 15.41	89.12 ± 16.41	>0.05
							FVC, %	91.88 ± 16.46	91.73 ± 16.04	
							VC, %	98.18 ± 15.80	100.0 ± 10.98	
							DL_{CO}, %	89.43 ± 15.26	86.69 ± 16.06	
Clin *et al*., 2011	2,743	403	Asbestos workers	France	CEI (exposure units x years)	No PP: 47.9 ± 83.1 With PP: 112.6 ± 128.6	FEV_1, %	**101.9 ± 19.2**	**97.9 ± 19.4**	**0.0032**
							FVC, %	**100.4 ± 16.6**	**96.6 ± 16.6**	**<0.0001**
							FEV_1/FVC	80.0 ± 7.9	79.2 ± 9.0	0.27
							TLC, %	**101.2 ± 16.0**	**98.1 ± 14.2**	**0.0494**
Spyratos *et al*., 2012	266	29	Cement factory workers	Greece	Mean concentration	1.7-6.49 f/ml	FEV_1, %	99.8 ± 15.2	92.6 ± 14.3	0.461
							FVC, %	99.6 ± 13.8	94.3 ± 12.5	0.536
							FEV_1/FVC	83.1 ± 10.4	78.1 ± 9.3	0.294
							MMEF, %	91.7 ± 30.4	71 ± 23.7	0.703
							TLC, %	93.3 ± 13	90.1 ± 7.7	0.983
							DL_{CO}, %	101.3 ± 15.8	100.5 ± 20.3	0.844

Notes:
Statistically significant results are in **bold** type.
CEI = cumulative exposure index; DL_{CO} = diffusing capacity for carbon monoxide; eCO = exhaled carbon monoxide (a marker of lung oxidative stress); FEF_{50} = flow at 50% of forced vital capacity; FE_{NO} = fractional exhaled nitric oxide (a marker of lung oxidative stress); FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; HRCT = high resolution computed tomography; MEF = forced expiratory flow at the level when 50% of the FVC remains exhaled; MEF_{25-75} = forced expiratory flow at the level when 25-75% of the FVC remains exhaled; MVV = maximal voluntary ventilation; NR = not reported; PP = pleural plaques; RV = residual volume; TLC = total lung capacity; TL_{CO} = transfer factor for carbon monoxide; VC = vital capacity.
(a) Presence of pleural plaques was evaluated as an independent variable.

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