HHS Public Access

Author manuscript

Ann Occup Hyg. Author manuscript; available in PMC 2015 November 01.

Published in final edited form as:

Ann Occup Hyg. 2014 November ; 58(9): 1205–1208. doi:10.1093/annhyg/meu058.

Human and Animal Evidence Supports Lower Occupational Exposure Limits for Poorly-Soluble Respirable Particles:

Letter to the Editor re: 'Low-Toxicity Dusts: Current Exposure Guidelines Are Not Sufficiently Protective' by Cherrie, Brosseau, Hay and Donaldson

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We commend the overall evaluation by Cherrie *et al.* (2013) of the current occupational exposure limits (OELs) for respirable poorly-soluble low toxicity (PSLT) particles. As described in that paper, the epidemiological studies provide compelling evidence that exposure to PSLT at the current OELs has been associated with adverse health effects, including pulmonary fibrosis and lung function deficits. In contrast to Cherrie *et al.* (2013), we discuss here that the chronic inhalation studies in animals also provide evidence of the adverse pulmonary effects of PSLT.

For example, we would like to clarify or correct the following statements (p. 688, 2nd column):

> (1) …the phenomenon of rat lung overload has little relevance for human lung response at high lung burden of low-toxicity dust.

This statement is not entirely supported by the scientific evidence. While it is correct that differences have been observed in the rat and human lung clearance and retention kinetics for respirable particles, these differences have been well described, and can be accounted for, using lung dosimetry models in humans (Kuempel *et al.*, 2001a,b; Gregoratto et al., 2010, 2011) and rats (Tran et al., 1999, 2000; Anjilvel and Asgharian, 1995). Because of the

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slower pulmonary clearance in humans, particles can build up in the lungs at exposures below those that would cause overloading in rats (Snipes, 1989; Kuempel *et al*., 2000; Kuempel and Tran, 2002). This build up is associated with the movement of particles into the alveolar interstitium of the mammalian lungs (Nikula et al., 1997, 2001). Only at overloading do the particle lung burdens in rats reach the higher levels that have been reported in coal miners, i.e., up to 10 mg g^{-1} lungs or more in rats (Morrow, 1988; Muhle *et al.*, 1990; Bellmann *et al.*, 1991; Oberdörster *et al.*, 1992) and in humans (Attfield *et al.*, 1994; Kuempel *et al.*, 1997; Tran and Buchanan, 2000).

In addition, the lung responses to these high lung burdens of PSLTs can be qualitatively similar in rats and humans (Castranova, 2000; Attfield *et al.*, 2012). As described in Cherrie (2013), the lung inflammatory and fibrotic response to PSLT has been observed to be greater in rats than that in mice or hamsters (Bermudez et al., 2002, 2004; Elder *et al.*, 2005). Consistent with a persistent inflammation and cell proliferation mode-of-action, rats (but not mice or hamsters) showed increased lung cancer response to chronic inhalation of PSLT particles (ILSI, 2000; Schins and Knaapen, 2007). Yet, studies in mice and hamsters were negative for some particles that have been classified as known human carcinogens (Mauderly, 1997). The proportion of lung tumor types has been observed to differ in humans and rats exposed to respirable particles (ILSI, 2000), although some of the differences may be due to smoking-related tumors in humans and terminology differences (Maronpot *et al.*, 2004; NIOSH, 2011b). An ILSI (2000) expert panel concluded that the rat is a useful model for non-neoplastic lung responses to poorly-soluble particles and that (in the absence of mechanistic data to the contrary) it is also relevant to identifying potential carcinogenic hazards in humans.

A comparative pathology study (Green *et al.*, 2007) showed that humans had a more severe centriacinar fibrotic response than rats exposed to silica or coal dust; while rats had a more severe intra-alveolar response (i.e., inflammation, lipoproteinosis, and alveolar epithelial hyperplasia) after chronic exposures to silica, talc, or coal dust. Yet in both species, silica and talc were more inflammogenic than coal dust, and the severity of response was associated with the dose (i.e., increased centriacinar fibrosis at high versus low coal dust). Thus, in humans a high dust load in the alveolar interstitium can lead to septal thickening and fibrosis even in the absence of an observed macrophage-mediated decline in clearance.

> (2) As discussed herein, high lung burdens of low-toxicity dust in humans cause COPD primarily and pneumoconiosis only in the very highly exposed coalmining populations (Kuempel *et al.*, 2001a,b).

In contrast to this statement that COPD and pneumoconiosis can develop ‘only in very highly exposed coalmining populations…’, significant risks of both COPD and pneumoconiosis have been predicted and observed in US coal miners exposed at the current US coal mine dust standard of 2 mg m^{-3} (and as low as 0.5 mg m^{-3}) over a working lifetime (NIOSH, 1995, 2011a; Attfield and Seixas, 1995; Suarthana *et al.*, 2011).

> (3) There is some evidence for the increased retention of dust in the alveolar interstitial compartment in the lungs of coalminers at the very high lung burdens they experience (Kuempel *et al*., 2001a,b; Gregorato *et al*., 2010).

This statement is only partially correct. In addition to the evidence from coal miners with relatively high dust exposures (Kuempel, 2000; Tran and Buchanan, 2000), the increased long-term retention of dust in human lungs has also been observed in workers with relatively low dust exposures (Gregarato *et al*., 2010Gregarato *et al*., 2011).

> (4) However, this is in contrast with the virtual cessation of clearance and subsequent rapid buildup of dust that accompanies rat lung overload, nor do we see the pathological consequences of rat lung overload – proliferation, fibrosis, and cancer – in humans.

The second part of this statement is inaccurate because the human lung responses to respirable particles can be similar to those observed in rats exposed to overloading doses of PSLT (as discussed above). Also, the related statement on p. 686 of Cherrie *et al.* (2013) that coal workers' pneumoconiosis (CWP) is characterized by 'minimal fibrosis (macules) and occasional nodule formation' is incomplete because it does not mention the severe form of CWP, progressive massive fibrosis – which is associated with disability and early death – or the evidence that both simple CWP and PMF are associated with significantly increased mortality from nonmalignant respiratory diseases (Attfield and Kuempel, 2008).

In addition, a quantitative comparison of rat- and human-based risk estimates for lung cancer associated with exposure to different types of poorly-soluble particles (coal mine dust, carbon black, titanium dioxide, or crystalline silica) shows statistically consistent risk estimates, given consideration of the imprecision in the animal and human data (Kuempel *et al.*, 2009; NIOSH, 2011b). An increase in lung cancer has also been observed in recent studies of coal miners in the USA (Graber *et al.*, 2014) and UK (Miller and MacCalman, 2010). Although the excess was most strongly related to silica in the UK study, it was most strongly associated with coal dust in the US study (in which the silica exposure estimates were also more uncertain).

In summary, we agree with Cherrie *et al.* (2013) that the epidemiologic literature provides adequate evidence that workplace exposure to PSLT has been associated with occupational lung disease and impairment at concentrations below the current OELs. This view has been accepted by some regulatory institutions. For example, in the USA, the regulatory exposure limit for respirable coal mine dust is to be reduced from 2 mg m^{-3} as a multi-shift average concentration to 1.5 mg m^{-3} as a single-shift (8-hr time-weighted average) concentration, starting in August 2016 (MSHA, 2014). In addition, the rat studies provide supporting evidence with qualitatively and quantitatively consistent findings to those in the human studies. Yet, more research is needed to reduce uncertainty about the rodent dose–response models compared to humans. Such evidence is important for risk assessment and OEL development of other types of airborne particles (e.g., nanoparticles) for which sufficient human data may not be available.

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