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Original Article

Risk Assessment for Metalworking Fluids and Respiratory Outcomes☆

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ABSTRACT

Background: Metalworking fluids (MWFs) are mixtures with inhalation exposures as mists, dusts, and vapors, and dermal exposure in the dispersed and bulk liquid phase. A quantitative risk assessment was performed for exposure to MWF and respiratory disease.

Methods: Risks associated with MWF were derived from published studies and NIOSH *Health Hazard Evaluations*, and lifetime risks were calculated. The outcomes analyzed included adult onset asthma, hypersensitivity pneumonitis, pulmonary function impairment, and reported symptoms. Incidence rates were compiled or estimated, and annual proportional loss of respiratory capacity was derived from cross-sectional assessments.

Results: A strong healthy worker survivor effect was present. New-onset asthma and hypersensitivity pneumonitis, at 0.1 mg/m^3 MWF under continuous outbreak conditions, had a lifetime risk of 45%; if the associated microbiological conditions occur with only 5% prevalence, then the lifetime risk would be about 3%. At 0.1 mg/m^3, the estimate of excess lifetime risk of attributable pulmonary impairment was 0.25%, which may have been underestimated by a factor of 5 or more by a strong healthy worker survivor effect. The symptom prevalence associated with respiratory impairment at 0.1 mg/m^3 MWF was estimated to be 5% (published studies) and 21% (Health Hazard Evaluations).

Conclusion: Significant risks of impairment and chronic disease occurred at 0.1 mg/m^3 for MWFs in use mostly before 2000. Evolving MWFs contain new ingredients with uncharacterized long-term hazards.

1. Introduction

Metalworking fluids (MWFs) are mixtures of diverse, potentially toxic materials that vary widely across process categories (milling, turning, grinding, stamping, etc.), within manufacturing facilities, across enterprises and over time, with continually evolving constituents. The routes of exposure are dermal, in the bulk liquid phase from parts handling and MWF splash and mist, and by inhalation of dusts, mists, and vapors. Over 800,000 workers in the United States in the 1980s were estimated to be routinely exposed to MWF in manufacturing and maintenance activities [1]. The exposures typically arise because MWFs are applied as spray or liquid stream to the surfaces where metal cutting or other process activities occur for the purposes of lubrication, cooling, and removal of chips or other cutting debris [2]. MWF systems exist in a range from large central systems with sumps containing tens of thousands of gallons (38,000s of L) of MWF, servicing dozens of operations, to small self-contained systems dedicated to a single machine. Operation of MWF systems includes filtration steps, tramp oil separation, and continual monitoring and adjustment of operating parameters such as pH, biocide levels, and lubricity [3]. There are four general classes of MWF: straight oils, soluble oils, synthetic, and semi-synthetic [4]. In this risk assessment, all types were treated as one generic entity because: (1) there is a wide diversity within those categories; (2) in many operations, environmental conditions are the result of multiple contributing sources of MWF; and (3) worker health recommendations likely would be nonspecific to MWF type. Risk assessments specific to MWF type would be more limited by sparse data than is the present assessment.

MWFs in the manufacturing environment provide rich media for microbial proliferation, sustaining a wide diversity of organisms

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in the bacterial, mold, fungal, and other orders [5]. Besides degrading the manufacturing process through pH excursions, corrosion facilitation, and obnoxious odors, they create a hazardous environment for workers. Biological debris such as endotoxins from degraded cell walls are ubiquitous in MWF systems and are a potent lung toxin causing compromise of lung function and sensitization. The use of biocides (themselves potentially toxic) in a variety of forms results in inhibition of microbial growth but also the accumulation of microbial remnants. In addition, some chemical ingredients of MWFs are themselves likely irritants or sensitizers such as tall oil fatty acids, colophony derivatives, diethanolamine, formaldehyde-releasing biocides, and other agents with specialized functions.

The health effects of MWF exposures have been reviewed extensively [6–10]. Respiratory disorders are a major category of MWF health effects appearing as reduced pulmonary function test (PFT) results, as well as specific and potentially life-threatening immune-mediated disorders: occupational asthma (OA) and hypersensitivity pneumonitis (HP) [7,11]. These latter outbreaks, although not common, can pose acute health emergencies and disrupt production through workforce displacement and MWF system rehabilitation. Because the causative agents are rarely known or measured before or during specific outbreaks of OA or HP, the exposures reported for such outbreaks are in generic terms such as current airborne MWF concentration, assuming that higher levels of MWF mist contribute to the dissemination of the causal agents that were present at that time. For some outbreaks, assessments with varying levels of detail on specific microbe involvement have been made [7,11].

In large industrial populations, the standardized mortality ratios (SMR) for nonmalignant respiratory disease (NMRD) typically range from 0.6 to 0.8 because of the strong *healthy worker effect* for NMRD [12]. Detailed investigations of exposure response (XR) for NMRD mortality and MWFs have not been reported; however, summary analyses—when the healthy worker effect is accounted for—reveal 15–30% excess NMRD mortality. In a survey of mortality in all Ford Motor Co plants 1973–1995, the SMRs for NMRD in assembly and stamping plants (environments not entirely free of respiratory hazards) were 0.75 (95% confidence interval [CI]: 0.69–0.81) and 0.78 (95% CI: 0.70–0.86), respectively, whereas in transmission and engine machining plants they were 0.88 (95% CI: 0.80–0.98) and 0.85 (95% CI: 0.74–0.97), respectively [13]. In a large mortality study of General Motors workers from three machining operations (transmission, gear, and axle), the overall SMR for NMRD during 1940–1994 was 879/935 = 0.94 (95% CI: 0.87–1.00) [14]. In both studies, mean employment duration was less than 20 years, implying that excess lifetime NMRD mortality could exceed 30–40% at MWF exposures which, in those years, mostly ranged from 0.5 to 3.0 mg/m^3 [14]. Also, contributing would have been less common exposures from welding, heat treat, forging, painting, and other operations. This MWF-associated NMRD mortality would have associated respiratory disease morbidity.

Dermatitis has been associated with MWF for more than two centuries and is a common complaint in metalworking environments, but the exposure is difficult to quantify, particularly as it involves bulk-phase contact through splash, spray, and manual handling of MWF-coated items as well as mist deposition. Some components of MWFs are well-known to be causative agents for dermatitis including allergenic substances also contributing to asthma. However, exposure attributes are usually not well-described and incidence studies are rare (Supplemental material, Table S8) [15–31].

The challenge for risk assessment is to generalize from findings in the specific worker populations that have been observed over several prior decades, as well as from animal studies usually limited to a few priority components of MWFs. The goal in this risk assessment was to describe respiratory impairment attributable to generic airborne MWF exposure conditions, based on published human studies.

2. Materials and methods

As part of a systematic review of MWF health effects for a National Institute for Occupational Safety and Health (NIOSH) publication, a literature search through 2014 was available using PubMed, ProQuest, Embase, CINAHL, NIOSHTIC-2, Compendex, Web of Science, and Scopus (contributing to this literature search was Oak Ridge Institute for Science and Education, Human Health Risk Assessment Team, Oak Ridge Associated Universities, December 2011). Search terms pertained to all the known reported health effects and included many terms used to denote MWF exposures. Because of the complex and changing compositions of MWF exposures, only total gravimetric measures of airborne mist or dust exposures to MWF are considered here for risk assessment purposes, in some cases with restriction to the respirable or thoracic fraction.

2.1. Asthma—HP

From 13 published accounts and 4 NIOSH Health Hazard Evaluations (HHEs), it was possible to derive estimates of OA or HP incidence for 28 groups of MWF exposed workers (Supplemental material, Tables S1, S2) [11,15–17,32–44] (HHEs are investigations in response to requests from concerned workers or employers mandated under the Occupational Safety and Health Act, 1970). In most studies, the period of observation could be delineated, and the population-at-risk and concentrations of airborne MWF could be approximately determined. For some, missing time periods (2 of 13 published studies) or exposure levels (5 of 22 groups) were stipulated based on the studies with known values and on general industry experience. New cases of HP and OA were combined in calculating incidence rates (IncRs) because they often occur together [16,42] and share immunologic etiology. For HP, a rare disorder, it can reasonably be assumed that all incident cases were attributable to the MWF environment. For new-onset asthma, in some published studies, the investigators identified the work-related cases, based on interview and history; in others, there was a comparison group unexposed to MWF for estimating a background incidence. In all HHE investigations, incident asthma cases were assessed for work-relatedness based on specific criteria. In the few studies, where work-relatedness of OA was not determined, this analysis assumes that half the apparent background incidence of OA was also work-related because there are other exposures in the comparison groups that potentially cause OA (e.g., in welding, painting, assembly).

The observed XR was found to decline with increasing average MWF air concentrations, implying a population-selection process as in the *healthy worker survivor effect* (HWSE). To estimate XR under minimal selection, a nonlinear regression model was fit on average MWF air concentration using iterative weighting to account for the uncertainty in the individual observed IncRs from the contributing studies (SAS proc nlin [45]; see Supplemental material for model specification). The model was: XR = a × exp (b × X), where *a* is estimate of XR as MWF exposure, *X,* approaches 0 (under minimal HWSE) and *b* is estimate of how fast HWSE changes with *X*.

The weighting used was the inverse variance of the observed IncR. Two very high outlying observations were excluded (XR > 0.5 per person-year per mg/m^3 MWF, observed at 0.07 mg/m^3 MWF). Also, excluded was the one observation based on a national surveillance cohort, which had a very high assigned weight because of the cohort size [17]. Unlike the others, this national cohort was not

assembled under outbreak conditions, would be expected to have a lower XR, and the exposures at the contributing workplaces were unknown.

The life-table approach in the BEIR VII report ("lifetime attributable risk") [46], which accounts for competing risks with onset of a discrete outcome, was used to calculate excess lifetime risk (XLTR). The exposure-response for asthma/HP incidence was applied to each year of age (more than 20 years) in a life table from the Social Security Administration [47] until age 65 years and the number of new cases of asthma/HP was subtracted each year from the surviving population. Summing the excess cases over all ages is an estimate, the excess numbers of cases that would occur as a result of a working lifetime (45 years) exposure at various concentrations under outbreak conditions.

2.2. PFT changes

Pulmonary function deficits were used to calculate annual proportional loss of respiratory capacity for use in a benchmark dose procedure [48]. Several investigations of pulmonary function have been carried out for populations of workers exposed to MWF with detailed exposure assessments. Two are cross-sectional analyses of *forced expiratory volume in one second* (FEV_1) and *forced vital capacity* (FVC) with a retrospective exposure assessment permitting estimation of cumulative exposure for different classes of MWF [32,49] (Supplemental material, Table S4); others are cross-shift studies observing acute effects of MWFs over the course of a work shift with estimates of current exposure [32,50] (Supplemental material, Table S5). The cross-sectional assessments used multiple linear regression models of loss in the outcome measure in liters (FEV_1), in relation to cumulative MWF exposure (mg/m^3-year) either as a continuous [49] or categorical [32] predictors. From the estimated parameter, one can derive the XR as the *excess annual proportional loss per unit of exposure*, EAPLX (Supplemental material, Table S4). For regression analyses estimating rate of loss, the baseline value of the outcome measure, if not reported in the study, was stipulated to be 3.8 L/sec for FEV_1, a typical value for healthy adult men.

Average values of EAPLX estimates across MWF types and the two studies were calculated as weighted means using weights as the inverse variance of the EAPLX estimates. The cross-shift analyses typically model a discrete outcome such as a fall in FEV_1 of 5% or more, using logistic regression and can be used in a benchmark dose procedure for discrete outcomes [48] (Supplemental material, Table S5). The summary, mean, EAPLX was applied in two different benchmark dose (BMD) procedures for continuous outcomes for estimating excess risk of pulmonary impairment. A traditional method assumes that the distribution of the outcome measure, such as FEV_1, is shifted toward smaller values with increasing exposure, maintaining the same dispersion (*SD*) [51,52]. Defining impairment as an observed FEV_1 falling below 80% of predicted (based on prediction equations [53]), one can calculate the additional proportion of impairment as a function of cumulative exposure. This traditional BMD procedure cannot readily be applied when impairment is defined as the *Lower Limit of Normal* (LLN) [53], which is the clinically preferred definition, because a 20% deficit represents different impairment prevalence across age groups. An alternate method uses the NHANES III population on which the Hankinson et al LLN prediction equations [53] were based to estimate what exposure over 45 years would cause an individual to fall below their LLN, again using the regression-derived XR estimates, and counting how many of the population would then fall into the impaired range as a function of MWF cumulative exposure. The reported findings on the cross-shift fall of FEV_1 were not used for risk assessment because the clinical significance of the largely reversible cross-shift changes for risk assessment is unclear and long-term studies to resolve this issue do not exist. Declining pulmonary function has also been observed to be a risk factor for mortality independent of age, gender, race, smoking, and body mass index. Five studies analyzed mortality and current FEV_1 [54–58], three of which provide estimates of rate ratios that can be applied in a life-table analysis of excess lifetime mortality risk [54,55,57] resulting from pulmonary impairment.

Respiratory and related symptoms of mucosal irritation are common among workers exposed to MWF, but there are also symptoms potentially related to HP (fever, chills, headache, dry cough, flu-like symptoms, and malaise) and asthma (shortness of breath, chest tightness, and wheeze). The natural history of MWF-associated symptoms with sustained exposures has not been adequately investigated; these symptoms are potentially sentinel effects predicting long-term and possibly irreversible respiratory and other changes. Symptom prevalence was reported in both published studies and HHEs (Supplemental material, Tables S6, S7 [15,16,18–21,32,33,35–37,59–68]. In some cases, symptoms were identified as "work-related," and no comparison group reported. When a control group was not identified, but a relative risk measure reported, the specific symptom prevalence (representing baseline risk) in the MWF-unexposed group was stipulated based on average prevalence for that symptom across all reporting studies. Because there are other exposures in the local comparison groups that potentially cause respiratory and other symptoms (e.g., in welding, heat treating, testing, painting, assembly), this analysis assumes as with OA that half of the apparent background symptom prevalence (no MWF exposure) is also work-related. Although not an adequate basis for quantitative risk assessment, for descriptive purposes, excess prevalence per unit of current average facility MWF exposure was calculated across all reported symptoms. Then a weighted nonlinear regression (using the same model as for asthma/HP) was calculated with respect to average facility exposure to estimate prevalence at low MWF exposures. The excess prevalence at higher exposures was calculated by linear extrapolation of the odds (excess prevalence = excess odds/[1 + excess odds]).

3. Results

3.1. Asthma—HP

Episodes from published studies and HHEs were combined and IncRs for attributable outcomes calculated (Fig. 1). The IncR generally declined across studies with increasing average current MWF exposure level. Assuming that the risk of onset was not cumulative with respect to exposure, XRs were obtained by dividing attributable IncRs by facility average (current) exposure concentrations. When plotted against average MWF exposure concentrations, there was a distinct decrease in the XR with increasing average MWF airborne concentration (Fig. 2). The decline in exposure-response with increasing average MWF air concentration could have several possible explanations: (1) a strong dose-rate effect (lower exposures having a larger response than expected based on a linear relationship); (2) a strong survival selection effect: workers with developing sensitization are less likely to remain in employment and be identified, or susceptible individuals (such as atopic) may be less prevalent in higher MWF exposure environments; (3) increased underreporting of new cases with longer periods of follow-back (suggested by inverse association of duration and IncR; Supplemental material, Table S3); and (4) over longer periods, a lower proportion of the observation time pertains to actual outbreak conditions causing fewer asthma or HP episodes compared to shorter periods where an active episode was usually

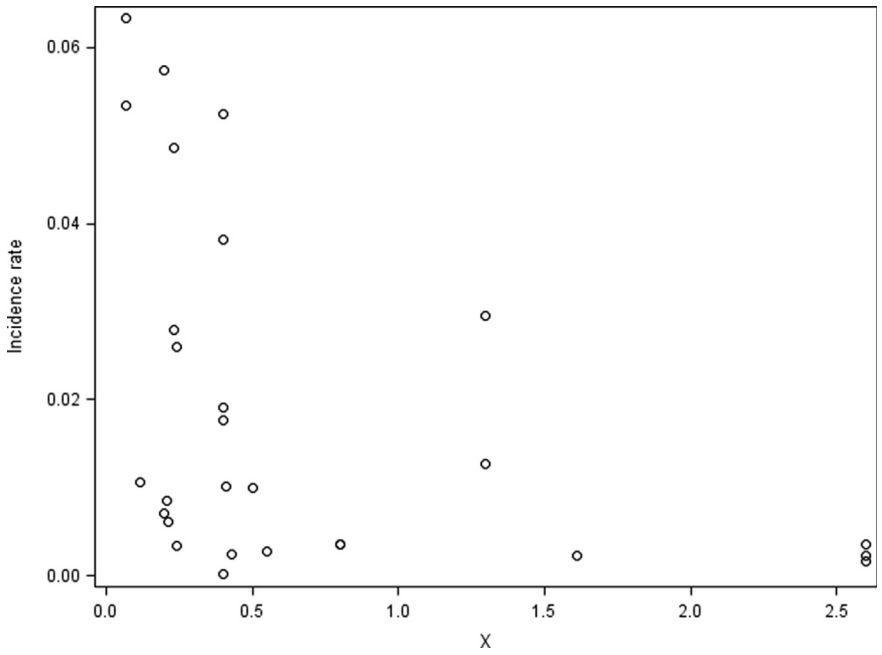

Fig. 1. Annual incidence rate of occupational asthma (OA) and hypersensitivity pneumonitis (HP) (new cases per person-year) on current exposure (X, mg/m^3) from published studies and Health Hazard Evaluations (HHEs).

the stimulus for the investigation. There is abundant evidence for worker survivor bias in studies of OA as reviewed by Le Moual et al [69].

To estimate the XR in the limit of low exposure (where dose-rate is highest or selection least), an iteratively weighted nonlinear regression curve was fit with a model that assumes an exponential decline in XR with increasing MWF concentration (Fig. 2). The intercept from this model yielded an XR of 0.136 cases per person-year per mg/m^3 MWF (95% CI: −0.002,0.27), conditional on being in an environment experiencing an HP or OA outbreak. The study reporting the lowest incidence, which was excluded [70], was based on national databases in which ascertainment had no direct connection to reported episodes. The XLTR of incident OA or HP, conditional on being in an environment experiencing an HP or OA outbreak, was calculated by applying the estimated XR in the life-table procedure. This assumes that the health effects are irreversible under continuing exposure and new cases are removed from follow-up. Under continuous causative conditions over a working

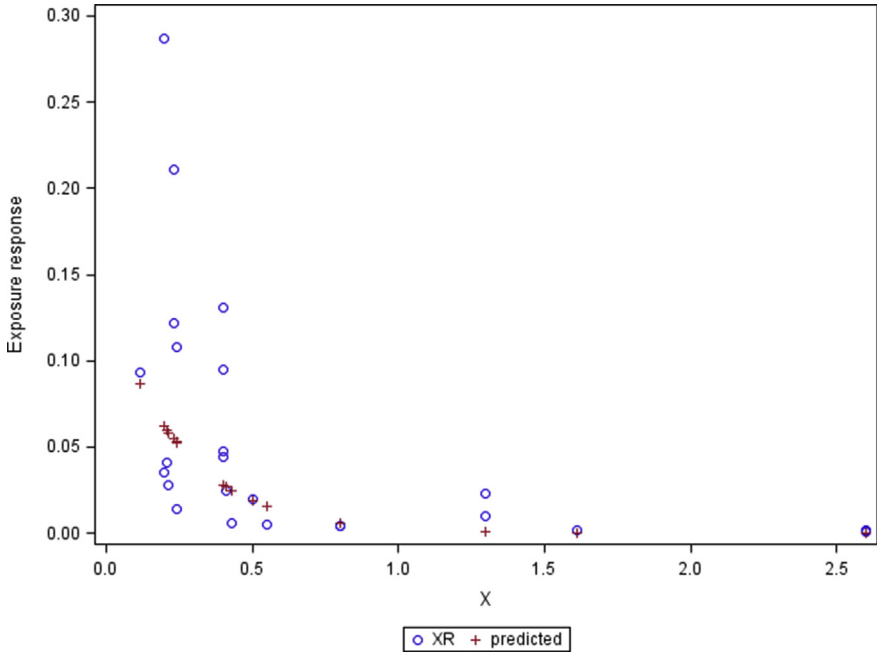

Fig. 2. Fitted prediction curve for XR for OA and HP on current exposure (new cases per person-year per mg/m^3) from published studies and HHEs by weighted nonlinear regression. XR, exposure response.

Table 1
Excess lifetime risk (per thousand, constant MWF exposure over 45 years) for asthma/HP onset in MWF populations under outbreak and 5% prevalence of outbreak conditions: published studies and HHEs

MWF exposure (mg/m^3)	Excess lifetime risk (per 1000)	
	Outbreak conditions	Assuming 5% outbreak prevalence
0.5	945	140
0.2	700	59
0.1	453	30
0.05	260	15
0.02	114	6
0.01	59	3
0.005	30	1.5
0.002	12	0.6
0.001	6	0.3

HHE, Health Hazard Evaluation; HP, hypersensitivity pneumonitis; MWF, metalworking fluid.

lifetime (45 years), workers exposed at 0.1 mg/m^3 MWF would have a 45% risk of acquiring OA or HP (Table 1); at 0.01 mg/m^3 MWF, they would have a risk of 5.9%. If one were to postulate that prolonged microbiological conditions in MWF systems giving rise to new cases of OA or HP have only a 5% prevalence in general metalworking environments; then at 0.1 mg/m^3 MWF, the XLTR would be 3% and the exposure for one-per-thousand risk would be about 0.003 mg/m^3 MWF (Table 1).

3.2. Pulmonary function changes

In the two published studies with sufficient summary data [32,49], bias from an HWSE could not be assessed. Assuming no dose-rate effect (i.e., that brief high exposures have the same effect as longer-duration low exposures with the same cumulative exposure), the mean annual proportional loss in pulmonary function per mg/m^3 MWF was calculated to be 0.0049. Applying the benchmark dose procedure resulted in estimated excess prevalence of impairment (falling below 80% of predicted FEV_1) at a specified current MWF exposure for 45 years (Table 2; see Supplemental material for benchmark dose coding). At 0.1 mg/m^3 MWF, the excess prevalence was about 2.7 per 1000. Defining impairment using the clinically more appropriate LLN [53] produced a similar excess prevalence, 2.4 per 1000 (Table 2; see Supplemental material for BMD coding). The estimates from the two benchmark dose procedures were quite close but the age distributions of excess impairment would differ. The benchmark dose procedure was applied only for FEV_1 because FVC were FEV_1 are correlated and FEV_1 is a standard evaluation tool for occupational respiratory disease. The excess annual proportional losses were similar for FEV_1 and FVC (Supplemental material, Table S4). These BMD estimates, based on cross-sectional regression analyses, assume that the effects are irreversible: the additional proportion of the population that would become impaired after 45 years at a fixed exposure; they do not account for competing risks, such as death. Based on the previously reported relationship between declining FEV_1 and overall mortality [54,55,57], the XLTR of mortality from respiratory impairment attributable to MWF was predicted to be 2.1 per 1000 at 0.1 mg/m^3 MWF (Table 2).

As with the asthma and HP IncRs, the excess prevalence of specific symptom complaints (such as shortness of breath, wheeze, or cough) declined in the published studies (above 1 mg/m^3 MWF) and in the HHE reports (above 0.3 mg/m^3 MWF) (Supplemental material, Figs. S1, S3). Excess prevalence per unit of MWF exposure also declined (Supplemental material, Figs. S2, S4), consistent with the selection hypothesis suggested in the asthma/HP data, but this would result even without an HWSE because with increasing exposure intensity, excess prevalence cannot exceed 1.0. The weighted regression identified the intercept representing symptom XR for low concentrations where the HWSE would be minimal. In the HHE investigations, which typically result from worker complaints and requested investigations, the exposure range (up to 0.6 mg/m^3) was lower than in the published studies (up to 3.2 mg/m^3) but the symptom XRs were higher (Supplemental material, Figs. S3, S4). Because the predicted excess prevalence per unit MWF (at low concentrations) was a good approximations of the predicted odds of attributable symptoms, the excess prevalence associated with higher exposures was obtainable by scaling the odds linearly to higher exposures and then obtaining prevalence as odds/(1 + odds) (Table 3). At 0.1 mg/m^3, the predicted excess prevalence of a reported symptom in populations without HWSE was 0.046 or 5% in the published study populations and 21% in the HHE studies.

3.3. Dermal effects

The reported prevalence of a dermal disorder ranged from 0.10 to 0.85, but many of these studies are in response to acute outbreaks, as with HP. For this reason and because exposure is not generally defined, measured or reported, dermal effects are not a sufficient basis for a risk assessment. In regulating exposures on cancer risk or respiratory effects, however, it is likely that the controls resulting would substantially reduce dermal exposures as well through, e.g., enclosure and other engineering changes.

3.4. Summary risk assessment

The estimated risks for adverse respiratory effects associated with MWF exposures are displayed in Table 4. For asthma or HP

Table 2
Excess lifetime risk of pulmonary impairment or mortality (per thousand, over 45 years) attributable to cumulative (constant) MWF exposure, from cross-sectional studies with likely healthy worker survivor bias; by benchmark dose procedure (impairment) or lifetable analysis (mortality)

MWF exposure (mg/m^3)	Risk of falling below 80% of predicted FEV_1 or FVC (per 1000)	Risk of falling below the lower limit of normal FEV_1 (per 1000)	Excess mortality risk due to falling FEV_1 (per 1000)
0.5	12.5	12.1	10.6
0.2	4.9	4.5	4.3
0.1	2.7	2.4	2.1
0.05	1.6	1.3	1.1
0.02	0.9	0.4	0.4
0.01	0.6	0.16	0.21
0.005	0.5	0.16	0.10

FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; MWF, metalworking fluid.
Insufficient resolution using NHANES data.

Table 3
Predicted average prevalence of an attributable symptom (average across all symptom categories) associated with current MWF concentration, as derived from exposure response prediction equation

MWF exposure (mg/m^3)	Published papers	NIOSH Health Hazard Evaluations
0.5	0.193	0.565
0.2	0.087	0.342
0.1	0.046	0.206
0.05	0.023	0.115
0.02	0.009	0.049
0.01	0.005	0.025
0.005	0.002	0.013

Based on predicted excess prevalence per mg/m^3 MWF evaluated at facility average MWF concentration of 0.10 mg/m^3 reflecting relatively low degree of workforce selection and providing an approximation of excess odds from which excess prevalence at higher exposures was obtained as odds/(1 + odds) by linear extrapolation. MWF, metalworking fluid; NIOSH, National Institute for Occupational Safety and Health.

(and a 5% assumption on hazardous condition prevalence), the XLTR at 0.1 mg/m^3 MWF would be about 30 per 1000 (3%). Based on cross-sectional prevalence, attributable respiratory functional impairment would occur in 2.4 per 1000 at 0.1 mg/m^3 MWF (0.24%), but if an HWSE comparable to that observed for asthma/HP (Fig. 2) were present, the risk could be five-fold or higher, or >1.2%. At 0.1 mg/m^3 MWF, the estimated XLTR of mortality related to breathing impairment was 2.1 per 1000 (also subject to underestimation of the PFT effect).

4. Discussion

Exposure at 0.1 mg/m^3 MWF confers lifetime risks of adverse respiratory health effects (asthma/HP, PFT losses), including potentially fatal disease with sustained exposure, in the range 2–30 per thousand (Table 4) and could be considerably higher depending on the prevalence of outbreak conditions for asthma/HP (>5%) and the HWSE for PFTs. For comparison, in a 1998 review of MWF hazards, NIOSH compiled preventive practices and specified a recommended exposure limit (REL) of 0.4 mg/m^3 MWF (for the thoracic fraction), but this REL was not based on a quantitative risk assessment [7]. The estimates of associated symptom prevalence would encompass both acute and chronic effects. If some symptoms were somewhat statistically independent, then the predicted prevalence of one or more symptoms would be higher. The higher symptom prevalence in the HHE reports versus published studies could have resulted from more acute outbreaks being the focus of HHE investigations or possibly populations with different employment incentives, reporting disincentives, or tolerances for adverse effects.

This risk assessment treated all MWFs as a single generic entity. Type-specific MWF exposure limits would be based on more limited data, and the simultaneous presence of multiple MWF types would present difficulties in environmental assessments for compliance. The variability of respiratory hazard across specific MWF systems is possibly greater within-type than between types (at least among water-based MWFs). Microbial surveillance is another option for addressing immunologically mediated diseases but would be complicated and difficult to interpret with current knowledge; it might require biofilm sampling [41,71].

In a survey of HWSE manifest across many populations with OA, Le Moual et al recorded large effects (odds ratios 2–4) related to job changes associated with exposures and health effects [69]. The MWF HWSE was investigated in a re-analysis of survey findings at three automotive manufacturing plants [72] (some of the data pertaining to PFTs and symptoms in the present risk assessment came from those surveys). Taking into account worker job transfers in relation to MWF exposures, the investigators observed rate ratios of 4.0, 0.5, and 1.8 for straight, soluble, and synthetic MWFs, respectively, where previously estimated odds ratios ignoring HWSE were 1.0, 0.83, and 0.80 [72]. Those previous estimates were in conflict with the statistically significant increase in cross-shift FEV_1 decrements exceeding 5% [32,50], with relative risks ranging from 1.8 to 6.9 across MWF types (Supplemental material, Table S5). Furthermore, the symptom prevalence attributable to MWF (dyspnea, wheeze, chest tightness, and chronic bronchitis) across many studies is inconsistent with minimal or even protective effects on pulmonary function. Finally, there is the overall increase in NMRD mortality in MWF populations (Introduction) [13,14], which would not be accompanied by minimal or negative PFT impairment. In the larger PFT study [49] for this risk assessment, the mean exposure levels were in the range of 0.4–0.5 mg/m^3 where, in the asthma/HP incidence studies analyzed here, substantial HWSE was observed. The XR estimated here for asthma/HP with facility-average exposures of 0.5 mg/m^3 was a factor of 7 smaller than that estimated to occur without survivor bias (Supplemental material, asthma/HP: XR (0) vs. XR (0.5)). Therefore, the exposures corresponding to excess PFT lifetime impairment estimated here would likely be overestimated by a factor of at least 5 if the HWSE for PFT XR is comparable to that of asthma/HP incidence. These PFT findings are an indication of the daunting problems of cross-sectional

Table 4
Risk assessment for MWF exposure (per thousand): 45 years excess lifetime risk (mortality, asthma/hypersensitivity), 45 years excess prevalence by benchmark dose (PFT), and excess prevalence (symptoms)

MWF (mg/m^3)	Excess risk (per 1000)					
	Published papers			Published papers & HHE		HHE
	PFT < LLN	Mortality	Associated average symptom	Asthma/HP	Asthma/HP at 5% exposure[†]	Associated average symptom
0.5	12.1	10.6	193	945	140	565
0.2	4.5	4.3	87	700	59	342
0.1	2.4	2.1	46	453	30	206
0.05	1.3	1.1	23	260	15	115
0.02	0.4	0.4	9	114	6	49
0.01	0.16	0.2	5	59	3	25
0.005	0.16[‡]	0.1	2	30	1.5	13

LLN, Lower Limit of Normal; HHE, Health Hazard Evaluation; HP, hypersensitivity pneumonitis; MWF, metalworking fluid; PFT, pulmonary function test.
Conditional on the presence of episodic causative exposure conditions.
[†] Assuming 5% prevalence of episodic causative conditions.
[‡] Insufficient resolution using NHANES data.

assessments in the presence of HWSE: large costly and well-conducted studies are threatened.

4.1. Limitations

The analysis of OA and HP incidence is limited by the unknown identity of causative agents and their occurrence. The prevalence of sustained MWF conditions causing OA or HP in metalworking environments plausibly lies in the range 0.1–5% of metalworking environments, considering that less serious episodes may go unreported or even unrecognized. In this analysis, when work-relatedness of asthma was inferred from comparisons with workers unexposed to MWF, it was assumed that half of the incidence there was work-related. This assumption affected 6 of the 22 estimates of XR where exposures were <1 mg/m^3, the more important data points in estimating the intercept representing minimal HWSE (Fig. 2). A sensitivity analysis in which none of the asthma/HP cases in the MWF-unexposed group were assumed work-related, produced a slightly smaller intercept for the XR with minimal HWSE (0.121 vs. 0.136), but the model fit was inferior (*F* value: 6.74 vs. 12.75).

The BMD analysis for PFT does not account for competing risks, such as death, and may have slightly overestimated excess risk of impairment along with the underestimation due to HWSE. For MWF-associated pulmonary impairment to be an independent causal risk factor for mortality, requires the assumption that there are no other common medical conditions that independently increase mortality risk and diminish pulmonary function. Thus, the estimate of 0.2% excess mortality at 0.1 mg/m^3 MWF attributable to pulmonary function losses may be an overestimate (but also possibly underestimated due to HWSE).

4.2. Other MWF risk assessments

ICF Kaiser [73] examined pulmonary function data from several published studies [32,37,50,62] and an unpublished study (Greaves et al, 1996: Respiratory health of automobile workers exposed to MWF aerosols. III. Lung spirometry). Using data from Kennedy et al [50], they estimated that an MWF level of 0.39 mg/m^3 (Mondays) or 0.26 mg/m^3 (Fridays) would cause a cross-shift decrease in FEV_1 exceeding 5% in 10% of the population. The present work, based on two of the studies [32,49], estimated the 10% excess prevalence occurring at a higher MWF concentration: about 1.0 mg/m^3 (data not shown). Ten percent excess impairment (loss$\geq$5%) over a single workday [73], even if reversible, is of concern and occurred at MWF levels (about 0.5 mg/m^3) conferring 1.2% XLTR of pulmonary impairment (as analyzed here and underestimated). However, the cross-shift outcome was not used in the present risk assessment because of uncertain interpretation.

In an analysis of respiratory symptoms from Greaves et al [37], ICF Kaiser observed a decline in chronic bronchitis symptoms with increasing current exposure concentrations for the three major classes of MWF [73]. This observation is consistent with the diminishing XR identified in this risk assessment for multiple MWF-associated symptoms taken together. The ICF estimates of excess prevalence (at 0.2 mg/m^3) for the relatively serious symptoms of chronic bronchitis were 9–13% for various MWF types, slightly less than the 9% (published) and 34% (HHE) estimated here (Table 4).

4.3. OSHA guidance

US OSHA commissioned the earlier risk assessment by ICF Kaiser [73] and convened a working committee from industry, academia, labor, and government—the *OSHA Metalworking Fluids Standards Advisory Committee*—which performed an extensive review of the known health effects, current exposures, and industrial practices in controlling MWF exposures [74]. Most of the 15 committee members concluded that a permissible exposure limit (PEL) would be an appropriate component of MWF regulation ("The committee recommends a new 8-hour time weighted average PEL of 0.4 mg/m^3 thoracic particulate and 0.5 mg/m^3 'total' particulate. The scientific rationale for the recommended PEL is based on studies of asthma and diminished lung function"; https://www.osha.gov/dhs/reports/metalworking/MWFSAC-FinalReportSummary.html#START). The present risk assessment reflecting the experience of MWF-exposed workers before 2000, finds that generic MWF exposures at 0.1 mg/m^3 MWF (one-fourth of the current NIOSH REL) have associated attributable risks of 2–30 per thousand, which are higher than generally considered acceptable. In addition, changing MWF composition with evolving technology pose new, unknown risks [75].

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Conflicts of interest

The author has no conflicts of interest to declare.

Disclaimer

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Appendix A. Supplementary data

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