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Estimation of the probability of exposure to metalworking fluids in a population-based case-control study

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Abstract

We describe here an approach for estimating the probability that study subjects were exposed to metalworking fluids (MWFs) in a population-based case-control study of bladder cancer. Study subject reports on the frequency of machining and use of specific MWFs (straight, soluble, and synthetic/semi-synthetic) were used to estimate exposure probability when available. Those reports also were used to develop estimates for job groups, which were then applied to jobs without MWF reports. Estimates using both cases and controls and controls only were developed. The prevalence of machining varied substantially across job groups (10-90%), with the greatest percentage of jobs that machined being reported by machinists and tool and die workers. Reports of straight and soluble MWF use were fairly consistent across job groups (generally, 50-70%). Synthetic MWF use was lower (13-45%). There was little difference in reports by cases and controls vs. controls only. Approximately, 1% of the entire study population was assessed as definitely exposed to straight or soluble fluids in contrast to 0.2% definitely exposed to synthetic/semi-synthetics. A comparison between the reported use of the MWFs and the US production levels by decade found high correlations (r generally >0.7). Overall, the method described here is likely to have provided a systematic and reliable ranking that better reflects the variability of exposure to three types of MWFs than approaches applied in the past.

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Keywords

metal working fluids; exposure assessment; machining; bladder cancer; epidemiologic study

Introduction

Machining or metalworking fluids (MWFs) are used to control, through cooling and lubrication, heat produced during machining operations, which is important in achieving the desired size, finish and shape of the work piece. MWFs are complex mixtures that are generally classified into three or four types according to the amount of oil and water they contain: straight, soluble, synthetic and semi-synthetic (the latter sometimes combined with synthetic). Specific formulations may contain additives and differ not only among fluid types, but also by manufacturer and the specific purpose for which the fluid is intended. Once in use, the composition of the fluids may change further as a result of chemicals being added by the operator, contamination from being worked (i.e., metals and machining and hydraulic oils), and thermal degradation.

Several epidemiological studies have reported associations between cancer risk and metalworking fluids either as a group⁽¹⁻³⁾ or for individual MWF types⁽⁴⁾. Because of the differing formulations and contaminants, it is important to distinguish between MWF types to identify specific agents that may be responsible for the reported increased cancer risk. Many of the previous epidemiologic studies of MWFs were industry-based, and information on the specific type of MWF used was available from the company being studied. Population-based case-control studies differ from industry-based studies in that the former cover the entire working life of the study subjects, rather than employment at a specific company, and therefore all jobs are of interest. Because it is not feasible to contact all previous employers, the information used to assess exposures for population-based case-control studies is typically collected from the study subject. Exposure assessment in these types of studies is challenging because relevant information is generally limited to what study subjects can provide, whereas more technical information is often needed for accurate exposure assessments. For example, changes have occurred over time in the composition of MWFs (e.g., severe hydrotreating to reduce polycyclic aromatic hydrocarbons in the 1980s⁽³⁾ and elimination of metal nitrites⁽⁵⁾). These changes could affect disease risk. However, although study participants can provide information on the general characteristics of the MWFs they used, they cannot provide information on the chemicals that were present in those fluids. Therefore, we cannot assess exposure to specific compounds in this effort. It might be possible to investigate this issue in a cohort study where information may be available on use of specific MWF products or, based on reported calendar years of MWF use, in a case-control study.

An important step in the exposure assessment process is to estimate the likelihood that a subject was exposed to MWFs for each job that he/she held. Little information is available in the occupational health literature on the probability of MWF exposure for specific jobs. In this paper, we describe the published literature on MWF use. We present our approach for estimating the probability of exposure to the three types of MWFs among participants in a

population-based case-control study of bladder cancer in New England and the results of an evaluation of the probability estimates. Frequency and intensity estimates have also been developed for this study and are described elsewhere⁽⁶⁾.

Methods

Study Background

The New England Bladder Cancer Study population has been previously described⁽⁷⁾. Briefly, the study covered 1171 males diagnosed with urothelial bladder cancer from hospital or cancer registries in Maine, New Hampshire and Vermont from 2001-2004. Controls (n=1,418) were identified through state Department of Motor Vehicles (if under age 65) or beneficiary records from the Centers for Medicare and Medicaid Services (if over 64). The MWF analysis was restricted to men (895 cases, 1,031 controls) because few women were exposed to MWF.

The study population was enumerated using a protocol approved by the National Cancer Institute Special Studies Institutional Review Board, as well as the human subjects review boards of each participating institution. Each participant provided signed informed consent.

A questionnaire was administered that included information on topics such as demographics, diet, and lifestyle. The subjects were also asked to provide their work history (job title, employer, type of business, products made or services provided, dates, duties and activities, materials and chemicals used, and equipment and tools used) on all paid occupations lasting more than six months in response to open-ended questions. The jobs reported by the study subjects were held as early as the 1940s through the 2000s. If a subject identified a job, industry, activities or duties, materials or chemicals, or tools or equipment that *a priori* were linked through keywords with possible metal machining operations (On-line Supplemental Table I), one of seven job-specific questionnaire modules (electrician/electronic repair, mechanic, pipefitter/plumber, sheet metal worker, tool and die worker, welder, and machinist, hereafter called MWF modules) was administered. Only five modules of any type could be administered to a single individual and no module more than three times. The individual subject's jobs that were linked to a module were prioritized based on the longest job and the longest five (or three) jobs were triggered for receiving the module. The modules included the following questions:

1. On average, how often did you do any kind of machining or making of metal parts?
2. What kind of machining equipment did you use?
3. On average, how often did you use straight cutting oils or oils that look and feel like motor oil?
4. On average, how often did you use soluble cutting oils or oils that are milky white?
5. On average, how often did you use synthetic cutting oils or oils that feel like water and may be brightly colored, such as green or blue?
6. When you were machining or making metal parts, how many other metalworking machines were usually being used in the room where you machined?

7. What types of metals did you usually machine?
8. On average, how much time did you spend in a machine or maintenance shop?
9. On average, how much time did you spend in a production area of the plant?

The modules may be obtained from the corresponding author. The criteria for five modules and no more than three of one type were applied to minimize the length of the questionnaire. To further reduce burden on the subject, if a job was assigned to any MWF module other than machinist and involved fewer than 5 hr/wk of machining, questions 2-9 were not asked (see Direct Exposure to MWFs for how these jobs were assessed). No specific question was developed for semi-synthetic fluids because no characteristic was found that study subjects would have easily recognized, that indicated a high probability of use, and that distinguished semi-synthetic fluids from synthetic fluids. As a result, semi-synthetics were not assessed separately but were instead grouped with synthetics.

Literature Review

Our first step in the exposure assessment process was to conduct a comprehensive review of the literature on MWF measurements and use according to the methods described elsewhere^(8,9). We looked specifically for quantitative estimates of probability, production volumes, measurement data, and descriptive information on characteristics of the various fluids and recommendations as to which fluid types worked best with specific operations and metals.

Assessment of Probability of Exposure to Metalworking Fluids—Because investigators cannot investigate the actual fact of exposure in a population-based case-control study, it is important to estimate the likelihood of exposure. We define exposure here as being in a work area for at least 15 min/wk where at least one of the four types of MWFs was likely used, given that the work area was, or was likely to have been, a metal machining operation. We defined probability of this type of occurrence in relation to the MWF being actually reported by the study subject or the likelihood of that MWF being used in that decade, based on US production rates of the MWFs. We developed two types of probability estimates for each of the three types of MWFs: direct and indirect. In addition, each probability estimate was assigned a confidence score (scale of 1-4, with 4 being the greatest confidence) that indicated the relative confidence the industrial hygienist had in the probability estimate based on the specificity of the information reported by the subject. The estimates were developed for each job that had, or was likely to have had, machined, after reviewing responses to the questions in the occupational histories and MWF modules. Assignment of these metrics was hierarchical based on the available information. If a job was held across multiple decades, it could be assigned a different probability for the same MWF for each decade.

Direct exposure to MWFs—For jobs administered a MWF module (N=453), if the subject responded positively to using one of the MWFs (question (Q) 3, 4, or 5 above>0), a direct probability of 1.0 was assigned to the job with a confidence of 4 for that MWF (Table I). Jobs that machined (Q1>0) but were reported as not using a specific MWF (Q3, 4, or 5=0) were assigned a zero direct probability with a confidence of 1 for that MWF. If a

subject responded zero to metal machining (Q1) for a job (and therefore did not get Q3-5), a probability of zero was assigned to all MWFs; however, we assigned a confidence score of only 2 because the fact that a MWF module had been administered for this job caused some uncertainty that the job was truly unexposed. A probability of zero, with a confidence of 4, was assigned for synthetic/semi-synthetic fluids for the years before 1950, the first year synthetics were manufactured (semi-synthetic fluids were developed after this time).

A number of other (likely) metal machining jobs did not have machining information because no MWF module had been administered, mainly because the job did not meet the module selection criteria (above). In addition, some respondents (e.g., managers, janitors) received modules unrelated to machining but indicated that they worked in an area with a possible metalworking machining operation. Therefore, an industrial hygienist reviewed all information reported on all jobs by all study subjects to determine whether any were likely to have involved machining or work in a machining area. Some responses to the industry (e.g., made metal products) and job title (e.g., machinists, maintenance workers, mechanics, farmers, and some construction workers) questions identified jobs that may have been associated with machining operations. Responses to the questions on activities/duties (e.g., machined), tools/equipment (e.g., lathe) and materials/chemicals (e.g., "water-based machining fluid") also were used to identify jobs that might have involved machining. A total of 685 potentially exposed jobs without a MWF module was identified using these criteria.

For these 685 jobs, we had expected that the probability of use of specific MWFs could be inferred from the reported information along with information from the literature review on type of metalworking machine and metal. However, only 138 of the 685 jobs indicated the type of metalworking machine used, and of these 138, all but 67 of these identified more than one machine, making it difficult to identify a specific MWF (because MWFs tended to be used with particular types of metalworking machines). Only eight of these 67 jobs identified a metal, which also influences MWF selection. Moreover, machinists who answered Q7 reported working, on average, with four different metals (median=4.5; range=0-12, n=107). Therefore, we decided that it was not feasible to estimate probability of MWF exposure based on the type of metalworking machine and metal.

Instead, we developed a hierarchical approach for estimating the probability of exposure to each MWF type for these 685 jobs using information reported by study subjects for similar jobs that had received modules. The first step was to assign the 685 jobs, plus all jobs that had received a MWF module, to a job group: one of seven for which MWF use had been reported by at least one respondent: electrician, mechanic, plumber, sheet metal worker, tool and die worker, welder, and machinist, as well as four other possible machining job groups. By-stander was assigned to supervisory and technical workers (e.g., engineers) who were not generally expected to have machined but who may have been in a machining area. Production was assigned when the subject reported a job primarily performing non-machining production tasks in a machine products industry but that may have involved some machining or been in a machining area. Miscellaneous comprised jobs for which the tasks or location worked were unclear but which suggested a metalworking environment (e.g., apprentice in a boiler shop). These three job groups, although identified by these non-

machining labels, actually included a few respondents who reported machining in an erroneously administered MWF module and so were used in the imputation process. Finally, farmer was included as an eleventh group because equipment repair and maintenance, tasks that often involve machining, were reported in the farmer module; specific questions on machining, however, were not asked.

For each of these eleven job groups, we calculated the proportion of jobs that reported machining (# of jobs reported machining >0 hrs/wk/# of jobs reported machining 0 hrs/wk) based on those jobs with responses to Q1. The proportion was calculated across the study period within each job group.

Next, we extracted information from the literature on US production levels of straight, soluble, synthetic and semi-synthetic MWFs by decade in the 20th century. For each decade, we calculated for each MWF type its proportion (called herein MWF production proportion) of the total MWF production, combining synthetic and semi-synthetics for the reasons described above. A graph of MWF production figures from Figure 6.1 of Childers, 2006⁽¹⁰⁾ provided continuous data over 90 years. Because of the small size of the figure, the average production rate of all MWFs and of each MWF per decade was estimated.

We then assigned a direct probability of exposure to each type of MWF for each of the 685 jobs using a hierarchical approach. First, if the subject had reported machining (Q1>0) but Q3-5 were not asked or answered, the MWF production proportion(s) for the decade(s) the job was held was assigned, by decade, as the direct probability for each of the three MWFs, and 3 was assigned for confidence (Table I). Thus, if an electrician in 1955 reported machining 3 hours a week, the probability of exposure to straight fluid was the proportion of straight fluid in 1955 (0.40, Table II). A subject who reported not machining was considered for indirect exposure or exposure to mineral oil or was assigned a zero (see below). Next, if information on Q1 was missing, direct probability was calculated as the proportion of jobs that machined in the appropriate job group multiplied by the MWF production proportion for the decade the job was held. Thus, if the electrician in 1955 was missing information on machining, the proportion of electricians machining (0.14) was multiplied by the proportion of straight fluid in 1955 (0.40, Table II) to derive a probability assignment of 0.06. Confidence of these estimates was a 2. If a job was held across multiple decades, it could be assigned a different probability for the same MWF type for each decade.

For a small number of jobs (n=48), it was not clear which job group was appropriate because the subject appeared to performing tasks consistent with two job groups. For these jobs, the higher direct probability estimate of the two groups was assigned. All other jobs in the study were assigned a direct probability of 0 with a confidence (generally) of 3 or 4.

For estimation of probability as described above, we used all study subjects. Because of the possibility of recall bias, we also calculated the data for controls only.

Indirect exposure to MWF—Many of the respondents who indicated they did not use a MWF may have been indirectly exposed due to their presence in a machine or maintenance shop where machining was performed (hereafter called machine shop) or in a production

area of a metal products industry. We accounted for this indirect exposure by considering the time the job spent in a machine shop (Q8), the number of machines in the shop (Q6), the time spent in a production area (Q9), and the type of business and products made or services provided as reported in the occupational history.

For each job, we categorized the industry as being either a metal products or a non-metal industry. Each metal products industry was further sub-divided as automobile, automotive products or small jobs. These industries were identified because they were associated with measurement data in the literature and so were used in the development of exposure intensity estimates⁽⁶⁾. Each non-metal industry was subdivided into small (likely to have a small machine shop, such as a hospital) or other (likely to have a relatively larger machine shop, such as might be found in the paper industry).

For jobs with a MWF module, the median number of machines reported for each of the five types of industries was calculated from Q6. Ten machines was arbitrarily set as the minimum number required to be present for indirect exposure to occur because most jobs do not work an entire work shift in a machine shop and machines in such shops are often used sporadically. The medians for these five industry categories exceeded ten (range, 13-60), except for the small non-metal industry category (median=6). Thus, jobs for which subjects reported having worked in a machine shop (Q8) with at least ten machines (Q6) (regardless of industry type) were assigned an indirect probability of exposure to a MWF, based on the appropriate MWF production proportion and decade, with a confidence of 3 (Table I).

In addition, some jobs that did not machine were reported as being in a production area (Q9) of a metal industry. This work area could suggest the presence of metal machining operations (e.g., facilities manufacturing metal products, such as auto parts, turbines, sewing machines). These jobs were assigned an indirect probability of exposure to a MWF based on the appropriate MWF production proportion and decade, but with a confidence of 2. If the job did not involve work in a machine shop or in a production area suggesting machining operations (e.g., packaging), a probability of zero was assigned with a confidence of 2.

For jobs in the metal industry that received a MWF module, the proportion of jobs that spent time in a machine shop (Q8) or production area (Q9) was calculated for each of the ten job groups (farmers were not considered indirectly exposed because they generally work alone). These estimates of indirect exposure provided information for all remaining jobs in the ten job groups in the metal industry that did not receive a module or were missing the appropriate responses. Probability was assigned with a confidence of 1 as follows (Table I): 1) if the subject reported that the job spent time in a machine shop but the number of machines was less <10 or missing, the probability was based on the appropriate MWF production proportion and decade; 2) if the subject did not spend time in a machine shop and the response to Q9 was missing, the proportion of jobs that worked in a production area in the corresponding job group was multiplied by the appropriate MWF production proportion for the job's decade; and 3) if the response to Q8 was missing and the response to Q9 was zero or missing, the probability was based on the proportion of jobs in the corresponding job group that worked in a machine shop multiplied by the MWF production proportion for the job's decade.

Jobs in a non-metal industry for which subjects reported working in a machine shop with 10 machines were assigned the MWF production proportion for the job's decade with a confidence of 3 (Table I). If the response to machine shop time was zero, a probability of 0 was assigned with a confidence of 2. For all other jobs in a non-metal industry, probability of indirect exposure was estimated, with a confidence of 1, as follows: 1) if the time in a machine shop was greater than zero but the number of machines was missing or <10, the MWF production proportion for the job's decade was assigned; or 2) if the response to machine shop time was missing and the job worked in the "small" subgroup, a probability of 0 was assigned. If the job worked in the "other" non-metals subgroup, the proportion of jobs that worked in a machine shop in the corresponding job group was multiplied by the MWF production proportion for the job's decade.

Similarly to direct exposure, if a job was held across multiple decades, the job could be assigned a different indirect probability for the same MWF for each decade.

Exposure to mineral oil—Mineral oil is contained in both straight and soluble MWFS and is also often a component of paints, cleaning agents and many other products. Therefore, all jobs assessed as having no direct and no indirect exposure to MWFS were assessed for possible mineral oil exposure (yes, no).

Evaluation of the Probability Estimates

It is important to evaluate retrospective exposure assessment methods to understand misclassification and error in the estimates. No data sources were found that contained the information needed for MWF use across all decades by operation. Industrial hygiene and epidemiology papers reporting MWF use were considered as a possible gold standard, but studies reporting specific MWFS were restricted to the 1990s, limiting their usefulness. In addition, as most studies were of the auto industry, they may not be appropriate to use as the gold standard for all industries because different industries use different metals and metalworking machines.

Our evaluation was based on a comparison, by decade, between (1) the proportions of jobs that had been reported as using the three MWFS (Q3-5) in each job group and (2) the mean production proportion of each MWF by decade. Because it was unclear if machinists (the job group with the largest number of subjects) used different machines or machined different metals than other job groups (because of possibly more complex parts, more exotic metals, or higher speeds), the proportions were calculated for both machinists alone and for all ten job groups that were reported to have used MWFS. To allow comparison with MWF production levels over time, the decade assigned to the Q3-5 responses was calculated as the midpoint of the span of years worked by the job. Spearman correlations also were calculated between the proportion of jobs reported to have used each MWF and the production proportions for each MWF.

Statistical Analysis

For jobs that received a MWF module, we present the number and proportion of jobs identified as having machined (Q1), as well as having used each of the three MWF types

(Q3-5), by job group. Because the probability of exposure in a job usually changed from one decade to the next, for presentation purposes, a job was assigned its highest probability for each MWF. If a subject had two jobs in the same job group (e.g., mechanic) and the jobs' dates resulted in the subject being in different probability categories for the same MWF (because the jobs were held in different decades), each job was counted with its highest probability. Thus, subjects may have been counted multiple times in this analysis. We also calculated the number and proportion of jobs identified as having worked in a machine shop (Q8).

The number and proportion of jobs, subjects and exposed years were also calculated for the entire study population, including jobs that did not receive a machining module and jobs considered not exposed. As above, if the job had multiple probabilities for a MWF because the job spanned multiple decades, we identified in the table its highest probability for that MWF. Each subject, however, was counted only once for each MWF, based on the highest probability of exposure across all jobs. Finally, for each subject/MWF a year was counted once based on the highest probability across all jobs held in that year (some subjects reported more than one job for some years). For presentation purposes, three categories of probability are identified: possible (>0 - 0.49), probable (0.5 - <1.0) and definite (1.0) because these were the categories used in the epidemiologic analysis⁽¹¹⁾.

Results

Literature Review

Mean production figures from Figure 6.1 of Childers, 2006⁽¹⁰⁾ and the proportion of each MWF produced by decade are provided in Table II. Descriptions of the fluids are presented in Table III. Recommended fluids are presented for various types of machining operations and metals by decade (On-line Supplemental Table II). A summary of this information is presented below.

Straight fluids—Straight fluids are petroleum or mineral oil-based fluids that contain no water and feel like motor oil (Table III). They have been produced since before the 1910s and therefore have tended to be found most often with older machines. Since the 1970s, these fluids have been severely hydro-treated or solvent-refined to reduce the polycyclic aromatic hydrocarbon (PAH) content. Straight fluids had been the most produced fluid type until around the mid-1940s, when production started to decrease, falling to 25-40% of all fluids in the 1950s and 1960s, about 15-20% in the 1970s and 1980s, and $<10\%$ in the 1990s (Table II)⁽¹⁰⁾.

Straight fluids are limited to low temperature and low speed operations that require fine surface finishes⁽¹²⁾ (On-line Supplemental Table II). These operations need a considerable amount of lubricity to reduce friction⁽¹²⁻¹⁴⁾ because of the cushioning effect necessary between the work piece and the cutting tool^(14,15). Their use has been largely restricted to heavy-duty machining and grinding operations such as broaching, tapping, threading, gun drilling and grinding⁽¹⁶⁾.

Although straight fluids are less popular than in the past when they were used particularly for nickel, cobalt, and magnesium⁽⁵⁾, they are still preferred for severe and extremely severe metalworking operations for most metals (On-line Supplemental Table II). This is especially true for the more difficult to cut metals such as certain stainless steels and super-alloys⁽¹⁴⁾. Extreme-pressure additives (e.g., chlorine, sulfur, phosphorous, and polymer lubricants) have been added for the more severe operations that require greater lubricity at higher temperatures and pressures⁽¹⁵⁾ (On-line Supplemental Table III). Use of straight fluids for severe and moderately severe operations has become less frequent over the years, and there have been few operations of light severity for which straight fluids have been recommended.

Water-soluble fluids—If water is added to the fluid, the MWF is a soluble, synthetic, or semi-synthetic fluid. Water is added to move heat away from the machine and work piece because, as the cutting speed increases, cooling is a higher priority than lubricity. Water has extremely poor lubricating properties and can cause severe corrosion to ferrous (and many nonferrous) metals⁽¹⁶⁾. The cooling ability among water-soluble fluids is generally greatest for synthetic fluids, followed by semi-synthetic fluids and then soluble fluids^(14,16). Additives in these fluids (e.g., chlorine, phosphorus, and sulfur) combine water's cooling abilities with lubricity, thereby reducing corrosion on machine tools and work pieces (On-line Supplemental Table II). Thus, similarly to straight fluids, extreme-pressure additives have been added to water-soluble fluids for severe operations requiring greater lubricity at higher temperatures and pressures. Water-soluble fluids have been recommended more recently to replace straight fluids to eliminate oil mist, slippery floors, and fire hazards⁽¹⁷⁾.

Soluble fluids—Soluble fluids are composed of a base of petroleum or mineral oil combined with emulsifiers and blending additives in water. If the fluid is milky white, it is likely to be soluble (Table III). Production of soluble fluids started around the 1910s to improve the cooling properties and eliminate the fire hazard of straight fluids. By the 1940s, soluble fluids made up about half of the total fluid output⁽¹⁰⁾ (Table II). Their production continued to increase until the 1970s, when production started to decrease due to the use of synthetic fluids.

Soluble fluids have good lubricating properties due to their high oil content, but their cooling properties are not as good as those of synthetic and semi-synthetic fluids⁽¹⁶⁾. Soluble fluids were considered for many years as general purpose MWFs⁽¹²⁾ (On-line Supplemental Table II). They have been increasingly used to replace straight oils in extreme and severe operations due to the addition of extreme-pressure compounds in the fluids in the 1990s and 2000s. They can be used on both ferrous and non-ferrous metals, but have been used particularly on the latter (e.g., aluminum, copper, beryllium, and their alloys)^(14,18,19). They are generally suitable for applications where dissimilar metals such as aluminum and steel are present⁽¹⁹⁾.

Synthetic and semi-synthetic fluids—Synthetic and semi-synthetic fluids were first marketed because of their better cooling and rust protection properties, compared with soluble oils, in grinding operations. In addition, in the early 1970s, oil shortages encouraged fluid manufacturers to formulate synthetic, mineral oil-free products that could replace the mineral oil-based fluids⁽¹⁰⁾. Brightly colored fluids indicate synthetic fluids, but colors range

from transparent to milky white (Table III). Machines with enclosures that reduce the amount of fluid being dispersed into the general environment are also more likely to use synthetic fluids.

Synthetic fluids are 70-90% water, with the remainder comprising organic chemicals and additives combined to provide good lubricity. Because they contain no mineral oil, synthetic fluids are the best fluid for heat removal. Production of synthetic fluids began in the late 1950s⁽¹⁰⁾ (Table II). Less than 10% of the fluid volume produced in the 1950s was synthetic fluids, after which these fluids rose to about 20% of the market.

In the 1970s, synthetic fluids were used as general purpose fluids for both ferrous and non-ferrous metals⁽²⁰⁾ and were used for operations of extreme to light severity, depending on the metal (On-line Supplemental Table II). The simple synthetics were preferred for high-heat, high-velocity turning operations, due to their higher cooling capacity⁽¹⁴⁾. They were used for light and moderate severity processes of high-heat or high-velocity turning operations such as surface grinding, where heat removal is important to maximize grinding performance^(14, 16, 17). Over time, due to new additives, their range of operations increased to include extremely severe operations and harder-to-machine metals⁽¹⁴⁾. Complex synthetic fluids are now among the best fluids for heavy-duty cutting and grinding, especially on tough, difficult-to-machine, high temperature alloys^(14, 16, 19).

Semi-synthetic fluids are essentially a hybrid of soluble and synthetic oils, combining the advantages of soluble oils (good lubricity, forgiving performance, good corrosion control) and synthetics (good cleanness and biological control)⁽¹⁷⁾. Production of semi-synthetic fluids began in the 1960s⁽¹⁰⁾ (Table II) when they contributed <10% of the output. Over the following decades, their production rose until in the 1990s they were about a third of all MWFs being produced.

Semi-synthetic fluids have the advantage of good cooling capacity, average lubricity and long sump life⁽²¹⁾, and they offer the wide performance range that is characteristic of water-soluble fluids (On-line Supplemental Table II). They have better cooling and wetting properties than soluble oils, allowing users to cut at higher speeds and faster feed rates⁽¹⁴⁾. Semi-synthetic fluids were primarily developed for the aircraft, nuclear and related industries⁽¹⁹⁾. A trend in the automotive and aerospace industry to lighter and stronger materials means that more aluminum, titanium, and alloy materials are now machined, compared to the traditional metals of cast iron and steel⁽¹⁷⁾, which increases the likelihood of semi-synthetic fluids' use. Specification of operations for semi-synthetic fluids, however, was relatively rare before 2000. By the 2000s, these fluids had a wide range of machining applications, including some extremely severe operations⁽¹⁴⁾. They were reported to work extremely well on all ferrous as well as non-ferrous metals, such as titanium, copper, brass, bronze and stainless steel, in both machining and grinding operations^(18,19).

Probability of Direct Exposure to MWF

The percentage of jobs that were identified as having machined varied substantially among job groups: less than a third of by-standers, electricians, plumbers and welders machined, compared to over 90% of machinists, production, and tool and die workers (Table IV). The

proportion of jobs in each job group that reported using straight and soluble oils, however, was fairly consistent (generally, 0.50-0.70). As expected, synthetic/semi-synthetic fluids were generally reported less frequently than the other MWFs (proportion=0.22-0.25). These proportions were used to estimate the probability of use for jobs that were not administered a MWF module. We recalculated these proportions, which were based on cases and controls combined, for controls only. There were some differences for job groups with at least five reports, but there was little difference in the overall proportion of subjects who reported machining (0.51 and 0.52, respectively), using any of the three MWF (0.63 vs. 0.56, 0.58 vs. 0.58 and 0.17 vs. 0.20 for straight, soluble and synthetic/semi-synthetic, respectively) or working in a machine shop (0.82 vs. 0.82) (On-line Supplemental Table IV). Using controls also appeared to have little impact on the distribution of the overall jobs, study subjects and exposure-years (On-line Supplemental Table V).

On-line Supplemental Table VI presents the number and proportion of jobs and subjects by probability level and job group. Across the entire population in the case-control study, about 7% of all jobs, 21-24% of all subjects and 8-10% of exposure years were assessed as having had some probability of exposure to each of the MWFs (Table V, possible+probable+definite). The category of possible exposure had the highest number of jobs, subjects, and exposure-years. Roughly 15-20% of the exposed jobs, subjects and exposure-years were classified as having definite exposure to straight or to soluble MWFs, based on having completed a module and reporting that the subject used these fluids (e.g., for straight-exposed jobs, 113/(602 possible+16 probable+113 definite)). About 5% were considered definitely exposed to synthetic/semi-synthetic fluids.

Jobs for which MWF modules were administered and were reported as having used straight fluids were relatively frequent prior to the 1950s; after the 1950s reported use was lower, but relatively constant over time (Table VI). US production of straight fluids, however, dropped dramatically, from 53% of the total MWF production <1950s to 9% in the 1990s. There was little pattern in the reports of soluble fluids for machinist jobs or for all job groups over time (0.58-0.79 and 0.55-0.80, for the two job groups, respectively). Production, however, fell slightly after the 1970s. In contrast, reports of synthetic/semi-synthetic use for machinist jobs generally increased over time, as they did for all job groups; the proportion of synthetic/semi-synthetic fluids produced in the US similarly rose. As a result, the prevalence of reported use by machinist jobs and by all job groups was generally in greater agreement with information on production for synthetic/semi-synthetic fluids than the other two MWFs.

The correlation coefficients between the proportion of machinist jobs that were reported using each of the MWFs and the corresponding production figures were 0.88, 0.71 and 0.85 for straight, soluble and synthetic/semi-synthetic fluids, respectively. For all job groups the correlation coefficients were 0.99, 0.05 and 0.87 for the three MWFs, respectively.

Discussion

Estimating the probability of exposure is useful in a population-based case-control study when it is not possible to determine with certainty whether exposure occurred, because probability reflects an estimate of misclassification⁽²²⁾. In this study, probability was

assigned based on the proportion of US production of each MWF type. Confidence was based on the quality of information provided by the study subject and informs a second source of misclassification. Levels of probability and confidence can be used in an epidemiologic analysis to exclude subjects that are likely to have more misclassification of exposure compared to other subjects. To our knowledge, no previous population-based case-control study has estimated the probability of exposure to the various MWF types used in machining operations.

We developed a hierarchical approach to estimating probability of exposure to the three fluid types used in machining operations. First, we asked study subjects if they machined and, if so, if they used the various MWFs by identifying not only the type of the MWF, but linking it to physical appearance, because visible and sensory perceptions are likely to increase the accuracy of the reports.

For many jobs, however, these questions were not asked. Probability had to be estimated to allow the retention or exclusion of these jobs in the epidemiologic analysis. The literature provided little direct information on the probability of exposure to the various fluids, and recommendations for fluids for various machining operations or metals sometimes overlapped for the same decade. Thus, incorporating information from the literature with the limited information from the open-ended questions to identify a particular MWF type was not straightforward. Also, changes in fluid type use and in the proportion of the MWF types being produced over time added to the complexity of the assessment. For example, in the 1960s, fluids were often metal-specific⁽¹⁶⁾. Since then the overall trend in fluid use has been to simplify operations^(23, 24) and decrease the number of fluids used. Thus, a plant in the 1960s frequently required as many as six to eight fluids with different formulations and additives, whereas in 1994, as few as two or three fluids may have been required to handle the same operations and work materials⁽¹⁶⁾. This change occurred because the composition of the fluids has become more varied and complex, resulting in today's fluids working well over a wide range of work materials and operations. In the auto industry in particular, fluids are required to be "universal" (i.e. able to be used not only with the more recently used aluminum, but with traditional auto materials such as cold-rolled and zinc-coated metals)⁽²⁴⁾. Therefore, it was not surprising that subjects with machining reports used multiple fluid types on a job or subjects with imputed information were identified with multiple fluid types (On-line Supplemental Table VII).

To add to the complexity, although recommendations of fluids for specific operations and metals were found, selection of a MWF type in a company may be based on several other criteria. These include applicability to the materials being worked, the machine tools, acceptability (the effect of the fluid on the operator's skin and the operator's acceptance of the fluid's odor, feeling, and appearance), machinability (the fluid's ability to generate the desired shape, size and finish on work materials while extending tool and wheel life)^(12, 16), environmental friendliness, cost, and disposability⁽¹⁶⁾.

In spite of the challenges in applying fluid use recommendations, we had expected to use the reported type of operation and the metal being machined as a basis for assigning probability. We found, however, that the study subjects typically reported using multiple machines and

metals. The literature describing metal machining, therefore, was not useful for our purposes, but it has been summarized here for other investigators where single machines or metals are reported.

Instead, we developed an approach that uses information on machining provided by other study subjects with similar jobs, and information from the literature on the proportion of each MWF produced by decade. There are several limitations to this approach. First, the information on MWF production applies only to US production, which may not reflect US consumption. The number of people using MWFs may not correlate with consumption because some workers may have rarely have used MWFS or used only a small amount. In addition, specific operations may still require a specific fluid type so that the fluid type used is not related to changes in its production. For example, straight fluids have been, and are still today, used for extremely severe processes such as lapping or tapping even though these fluids contribute little to the overall amount of MWFs manufactured. Information on such specific machining operations was limited for study subjects and therefore was not used.

We also were unable to distinguish synthetic from semi-synthetic fluid use because of the lack of different characteristics that would be recognizable to study subjects. Because the proportions of production rates of semi-synthetics were similar over time to those of synthetics, combining them is likely to have resulted in only random misclassification. Another limitation is that the additives and contaminants in MWFs have changed over time. If bladder cancer risk is associated with a particular MWF in the epidemiologic study, it will not be possible to identify which component may be causing the effect. A thorough investigation of all MWF additives and contaminants in a population-based case-control study is probably not possible.

Of the jobs that may have been exposed and were therefore eligible for a MWF module, about 5% did not receive a MWF module because the jobs did not meet the module selection criteria. In addition, for another 26%, a module other than a MWF module was administered. We could have administered the MWF modules for these jobs but chose not to in the interest of reducing the questionnaire administration time. Assigning varying levels of probability by job group likely reduced error compared with assigning the jobs to one of two groups, such as >50% or <50%, as has often been done in epidemiologic studies.

As is true for all population-based case-control studies, this study was dependent on self-reports. In our study, the reported job title, employer type of business, duties, and chemicals used were linked to the appropriate module through keywords used in the responses to open-ended questions. Open-ended questions can result in underreporting; however, because all jobs in the study were reviewed and assessed for MWF, lack of an assigned MWF module, or assignment of an incorrect MWF module, would have had little effect on the identification of a machining-related job. These variables, however, were also used in the assessment. Job title was used to assign the exposure group, employer type of business for information for the assessment of indirect exposure, dates for the decade of particular MWF use, duties for the performance of machining, and chemicals for identification of the MWF type used. Teschke et al. ⁽²⁵⁾ has reported good agreement for self-reported information on employer, job classification, dates, and duties (70-90%); however, overall validity of self-

reports of chemical agents was reported to be substantially more variable. Some of these self-reports, however, were based on open-ended questions; some were estimating relative exposure levels; and others had as the gold standard, expert review. We asked about the use of MWFs in closed-ended questions, which is likely to increase sensitivity while having only a small effect on specificity ⁽²⁵⁾. Those authors found substantially higher sensitivities and specificities for studies with closed-ended questions and a gold standard (i.e. knowledge of the particular workplace or biologic measurements) (>0.7). Teschke et al. ⁽²⁵⁾ concluded “It is incumbent on study designers to consider features which improve subjects’ reporting accuracy, including prompted questions about agents they can sense, using familiar terms common in worksite discourse...” We asked about fluid color and feel (Table III). We also used terms the subjects were likely familiar with. Workers who machine are generally considered skilled workers and are, therefore, more likely to know the type of MWF they were working with.

Another possible limitation with self-reports is recall bias. One source of recall bias is case status; however, we found little difference between the proportions of controls and all subjects who machined, used a specific MWF, or worked in a machine shop. In addition, a comparison of the reports of use by machinists and other job groups with production patterns over time showed similar trends for synthetic/semi-synthetic fluids, in that reported use increased over time. In contrast, reports of straight and soluble fluids were less consistent. In part, this lower agreement may have occurred because only the midpoint of the years the job was held was used to identify the decade. Most investigators, however, who have compared differences between cases and controls have found little or no difference in the validity of the reports ⁽²⁵⁾. In a sensitivity analysis, we found the difference to be minimal. Thus, recall error may have been limited. Moreover, since the epidemiologic analysis assigned all subjects to one of only two probability categories, <50% and >50%, any possible recall bias would have even less impact. The questionnaire did not ascertain changes in frequency over time; it may be that use of a particular MWF did not occur over the entire duration of the job. It may also be because the calculation of the production proportions was exclusive, i.e. the proportions of straight, soluble and synthetic/semi-synthetic fluids that were produced in the US had to equal 1.0 for any given decade. Subjects, however, were not required to select among the three fluids and often reported more than one. Finally, it may also be that the study subjects are not representative of the entire US, because the jobs were likely concentrated in New England.

Nonetheless, the correlation coefficients between reported use and production levels of specific MWFs were fairly high ($r = 0.7$). The one exception was the correlation between all job groups and production figures for soluble fluids. The low correlation ($r=0.05$) may be due to the lack of a trend and the low variability in the proportions of soluble fluids over time, both as reported by the jobs and as seen in the production rates. In contrast, the reporting and production of the other two MWFs had stronger trends and generally greater variability over time. The high correlations for straight and synthetic fluids and the small amount of change for soluble fluids suggest that the assignments were likely to result in little misclassification if production levels reasonably reflect overall use.

Strengths of this study include an objective and transparent, rule-based approach to assigning probability and confidence estimates. Specific information on MWF type was available for about 20% of the exposed jobs, which was then imputed to the remaining subjects by job group, allowing the probability assignment to reflect differences in machining among job groups. Indirect exposure and exposure to mineral oil was also evaluated. Along with the estimates of frequency and intensity⁽⁶⁾, the estimates of probability allow for investigation of multiple exposure metrics (e.g., cumulative, average, and highest exposure) in the epidemiologic study. Moreover, in the epidemiologic analyses, subjects with estimates of low probability and those with low confidence can be excluded because they are likely to introduce nondifferential misclassification into the analysis and thereby bias the risk estimates to the null. Finally, a comparison of the reported uses was made with independent data.

Conclusions

This study provided the basis for estimating the probability of exposure to the various metalworking fluid types used in machining operations when information on the specific fluids was not collected. The probability estimates were developed with estimates of intensity and frequency, which are the subject of another report. Alternative approaches to estimating exposure in population-based case-control studies have been to use duration of employment in a MWF-exposed job or a job-exposure matrix (JEM). Some investigators could consider the approach used here as a quasi-JEM, since subjects for whom we had no valid responses to the question on MWF use, we assigned probability based on the job reports of the study subjects. We believe, however, that development of probability, intensity, and frequency based on self-reports can better recognize differences in jobs than what is typically available from a JEM approach, as demonstrated by the variability shown here among the various job groups. We did not use a pre-existing JEM. Lavoue ⁽²⁶⁾ found very different prevalences between FINJEM and the Montreal JEM for oil mist (0.3 and 0.7 respectively), suggesting that selection of a JEM for oil mist is very important. This approach also allows for a greater investigation of possible exposure metrics. Overall, the method described here is likely to have provided systematic and reliable estimates that better reflect the variability of exposure to three types of MWFs than approaches applied in the past.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table I
Rules for Assigning Direct and Indirect Probability of Exposure and Confidence to Jobs
Possibly Exposed to Metalworking Fluids

Question Number and Condition ^A	Source of Estimate	Straight, Soluble, or Synthetic/Semi-synthetic Probability	Confidence
Direct Exposure			
Q3, 4, or 5: MWF Freq >0	Subject	1	4
Q1: MA Freq>0; Q3, 4, or 5: MWF freq=0	Subject	0	1
Q1: MA Freq=0	Subject	0	2
Q5: Synthetics <1950	Subject	0	4
Q1: MA Freq>0; Q3, 4, or 5: MWF Freq=. ^B	Subject and literature	MWF production proportion by decade	3
Q1: MA Freq=.	Job group and literature	Proportion of jobs in job group ^C with MA freq>0 * MWF production proportion by decade	2
Indirect Exposure			
OH ^D : Metal Industry			
Q8: mach shop >0; Q6: # machines 10	Subject and literature	MWF production proportion by decade	3
Q9: Prod area>0	Subject and literature	MWF production proportion by decade	2
Q8: Mach shop=0 and Q9: prod area=0	Subject	0	2
Q8: Mach shop >0; Q6: # machines <10 or .	Subject and literature	MWF production proportion by decade	1
Q8: Mach shop=0; Q9: prod area=.	Job group and literature	Proportion of jobs in job group with prod area>0 * MWF production proportion by decade	1
Q8: Mach shop=.; Q9: prod area=0 or .	Job group and literature	Proportion of jobs in job group with mach shop>0 * MWF production proportion by decade	1
OH ^C : Non-metal industry			
Q8: mach shop >0; Q6: # machines 10	Subject and literature	MWF production proportion by decade	3
Q8: Mach shop=0	Subject	0	2
Q8: Mach shop>0, Q6: # machines <10 or .	Subject and literature	MWF production proportion by decade	1
OH: Small industry Q8: mach shop=.	Professional judgment	0	1
OH: Other industry Q8: mach shop=.	Job group and literature	Proportion of jobs in job group with mach shop>0 * MWF production proportion by decade	1

Notes:

^A Q=question number. Q1: On average, how often did you do any kind of machining or making of metal parts? Q3: On average, how often did you use straight cutting oils or oils that look and feel like motor oil? Q4: On average, how often did you use soluble cutting oils or oils that are milky white? Q5: On average, how often did you use synthetic cutting oils or oils that feel like water and may be brightly colored, such as green or blue? Q6: When you were machining or making metal parts, how many other metalworking machines were usually being used in the room where you machined? Q8: On average, how much time did you spend in a machine or maintenance shop? Q9: On average, how much time did you spend in a production area of the plant? MWF=metal working fluid; MA freq=machining frequency; mach shop= machine or maintenance shop.

^B “. ”=missing.

^C Job group= electrician, mechanic, plumber, sheet metal worker, tool and die worker, welder, machinist, by-stander, production, and miscellaneous.

^D OH=occupational history

Table II
U.S. Proportion of Production Rates of Three Metalworking Fluid Types by Decade

Decade	Total MWF production, billion pounds	Straight (Prop)	Soluble (Prop)	Synthetic/semi-synthetic (Prop)
1910s	0.6	0.83	0.17	0
1920s	1	0.70	0.30	0
1930s	1.3	0.62	0.38	0
1940s	1.5	0.53	0.47	0
1950s	1.7	0.40	0.53	0.07
1960s	2	0.26	0.53	0.16
1970s	2.1	0.19	0.48	0.19
1980s	2.2	0.14	0.41	0.18
1990s	2.3	0.09	0.39	0.22

Notes: MWF=Metalworking fluids; prop=proportion of the US production. From: ¹⁰

Table III
Probability of Metalworking Fluid Use by Sensory and Operational Characteristics

Characteristic	Probability of fluid use			
	Straight	Soluble	Synthetic	Semi-synthetic
Oily like motor oil	High	No	No	No
Milky white fluid	No	High	Low	Low
Translucent or brightly color such as green or blue	No	No	High	Low
Used to dilute the oil	No	Moderate	Moderate	Moderate
Presence of old machines with underneath sump*	High	Low	Low	Low
Machines enclosed*	Low	Low	High	Low

* These characteristics reflect time trends in machine technology: older machines generally used straight fluids and newer machines, which tend to be enclosed, more likely use synthetic fluids.

Table IV
Frequency of Jobs Reporting Machining and Using Metalworking Fluids, by Job Group

Job Group	Q1 ^A : No. Jobs Machined (Prop) ^B	Q3: No. Jobs Used Straight (Prop)	Q4: No. Jobs Used Soluble (Prop)	Q5: No. Jobs Used Synthetic/ Semi-synthetic (Prop)	Q8: No. Jobs in a Machine Shop (Prop)
By-stander	3 (0.30)	1 (0.25)	2 (0.50)	1 (0.25)	10 (0.83)
Electrician	8 (0.14)	0	0	0	42 (0.66)
Machinist	91 (0.97)	60 (0.65)	62 (0.66)	20 (0.22)	99 (0.96)
Mechanic	27 (0.44)	11 (0.52)	11 (0.50)	0	54 (0.90)
Miscellaneous	5 (0.63)	4 (0.68)	4 (0.68)	0	11 (1.00)
Plumber	14 (0.26)	2 (0.50)	0	0	35 (0.59)
Production	5 (1.00)	1 (0.50)	0	0	5 (0.83)
Sheet metal worker	8 (0.42)	5 (0.63)	3 (0.38)	0	16 (0.89)
Tool & die	15 (0.94)	10 (0.71)	9 (0.64)	0	16 (1.00)
Welder	11 (0.28)	7 (0.78)	4 (0.44)	0	33 (0.81)
All	187 (0.51)	101 (0.63)	95 (0.58)	21 (0.17)	321 (0.82)

Notes:

^A Q=question number. See Table I. Based on responses to Q1, 3-5 and 8. Farmer jobs are not included because they were not administered any machining questions. The same data for controls only are presented in On-line Supplemental Table IV.

^B No.=number; prop=proportions calculated excluding jobs held <1950 (n=13) and do not include people with a job that was broken into 2 jobs (n=48). See text. Used with proportion of US MWF production (Table II) in the assessment of probability where information on metalworking fluid (MWF) use and machining was unavailable.

Table V
Frequency of Jobs, Study Subjects and Exposure Years by Metalworking Fluid Type and Exposure Category

Exposure Category ^A	Straight			Soluble			Synthetic		
	No. jobs (Prop) ^B	No. subjects (Prop)	No. E-Y (Prop) ^C	No. jobs (Prop)	No. subjects (Prop)	No. E-Y (Prop)	No. jobs (Prop)	No. subjects (Prop)	No. E-Y (Prop)
Unexposed	8488 (0.73)	621 (0.32)	54379 (0.69)	8487 (0.73)	622 (0.32)	54338 (0.68)	8541 (0.74)	634 (0.33)	54744 (0.69)
Mineral oil	2116 (0.18)	730 (0.38)	15648 (0.20)	2116 (0.18)	728 (0.38)	15664 (0.20)	2131 (0.18)	754 (0.39)	15750 (0.20)
Indirect	286 (0.02)	114 (0.06)	2599 (0.03)	291 (0.03)	122 (0.06)	2689 (0.03)	315 (0.03)	137 (0.07)	3100 (0.04)
Possible	602 (0.05)	368 (0.19)	5408 (0.07)	530 (0.05)	307 (0.16)	5016 (0.06)	578 (0.05)	367 (0.19)	5187 (0.07)
Probable	16 (<0.01)	15 (0.01)	40 (<0.01)	88 (0.01)	67 (0.03)	380 (<0.01)	33 (<0.01)	27 (0.01)	227 (<0.01)
Definite	113 (0.01)	86 (0.04)	1300 (0.02)	109 (0.01)	88 (0.05)	1287 (0.02)	23 (<0.01)	15 (0.01)	366 (<0.01)
Total	11621 (1.00)	1934 (1.00)	79374 (1.00)	11621 (1.00)	1934 (1.00)	79374 (1.00)	11621 (1.00)	1934 (1.00)	79374 (1.00)

For all study subjects, based on using all subjects' responses where data were missing. For the same presentation using only control responses where data were missing, see Online supplemental Table V.

Notes:

^A Possible =>0 and <0.5, Probable=0.5-<1.0, Definite=1.0 probability.

^B No.=number; prop=proportion.

^C E-Y=exposure years.

Table VI
Proportion of Reported Metalworking Fluid Use by Machinist Jobs and by Jobs Identified in the Eleven Job Groups and US MWF Production Figures by Metalworking Fluid Type^A

Decade (N Machinists/N All Job Groups)	Reports by Machinists			Reports by All Job Groups			Production figures		
	Straight	Soluble	Synthetic	Straight	Soluble	Synthetic	Straight	Soluble	Synthetic
<1950s (6/11)	1.00	0.60	0	0.77	0.55	0	0.53	0.47	0
1950s (25/56)	0.74	0.79	0.13	0.71	0.59	0.10	0.40	0.53	0.07
1960s (31/71)	0.65	0.78	0.18	0.66	0.65	0.14	0.26	0.53	0.16
1970s (29/46)	0.64	0.69	0.27	0.61	0.59	0.18	0.19	0.48	0.19
1980s (23/35)	0.65	0.72	0.36	0.57	0.59	0.22	0.14	0.41	0.18
1990s (11/24)	0.65	0.58	0.45	0.54	0.63	0.29	0.09	0.39	0.22
2000s (2/8)	0.67	0.67	0.33	0.56	0.80	0.14	NR ^B	NR	NR
Correlation coefficients with production figures	0.88	0.71	0.85	0.99	0.05	0.87			

Notes:

^A Farmers are not included because they were not administered a MWF module.

^B NR=Not reported