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LITERATURE REVIEW AND MEDICAL OPINION

SAIF Corporation
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ATTENTION: Holly O'Ddell
Attorney at Law

Dear Holly O'Dell:

Thank you for your request for a literature review which was completed by Rebecca Orwoll, M.D., Internal Medicine, Hematology and Medical Oncology.

I was recently asked to carefully review current scientific literature (in English only) and provide an annotated bibliography as well as comments in reference to support, or to lack thereof, for the hypothesis that female reproductive cancers, and cancer of the bladder, might be scientifically demonstrated to be caused by the exposures of firefighters. At hand is a discussion of the quantity and quality of scientific data to support, refute or postpone inclusion of select medical conditions in Oregon law as presumed due to firefighting, (barring strong evidence that other causes are more likely causative). More specifically are considerations to include "all female cancers" and "bladder cancer" in the Oregon presumption.

In the report I released on January 3, 2022, I stated that the data currently available do not clearly support that firefighting is causative of female reproductive cancers, for reasons discussed in that report, and discussed some of the nuance to that statement, and some of the challenges in the data. I also provided literature which was equivocal in reference to causality of bladder cancer by firefighters. For bladder cancer specifically, the time, meaning calendar dates, from which data were collected are relevant due to significant tobacco use in the past even by firefighters, such use now declining markedly in the United States; tobacco use data in these reports relevant but not always available; and advances in protective equipment which are both significant and important. For perspective, there are stronger data available for select

specific cancers, but overall, the risk of cancers of all types combined is in fact not increased in firefighters, based on available data.

Subsequent to that report, I have been asked to review the testimony of the Oregon State Firefighters Council and address the two studies and the opinions mentioned. https://www.oregon.gov/dcbs/mlac/Documents/2022/012822/LC96-OSFFC-follow-up-study-information.pdf

My prior review and testimony had included my analysis of the same two studies, and therefore I will add more detail here. It is my opinion that those two studies do not support a significant correlation between the occupation of firefighting and cancers of the female reproductive organs. As discussed below, the data in reference to bladder cancer are more nuanced, but not scientifically definitive, therefore my conclusions in my initial testimony remain unchanged.

I will begin with a discussion of the literature referenced by the Oregon State Firefighters Council, however further below is a discussion intended to help the reader not trained in science and statistics to better understand the complexity of the discussion. One might prefer to read that first.

I will now address the two studies mentioned in a letter provided to me by the Oregon State Fire Fighters Council, and the opinion in that letter:
https://www.oregon.gov/dcbs/mlac/Documents/2022/012822/LC96-OSFFC-follow-up-study-information.pdf

In the report by Laroche, Elena & L'Espérance, Sylvain. (2021). Cancer Incidence and Mortality Among Firefighters: An Overview of Epidemiologic Systematic Reviews. International Journal of Environmental Research and Public Health. 18. 2519. DOI: 10.3390/ijerph18052519., the authors stated, *"The results of the systematic reviews suggest that cancer incidence rates among firefighters do not differ significantly from that of a reference population."* Italics mine. Does this report support increased risk of female cancers or of bladder cancer, and if so, is this a definitive report to supplant other available data? Actually the data in Laroche's report include both positive and negative studies in reference to bladder cancer, and in all except one report, the confidence interval, which is a statistical tool to determine the likelihood that the results were due to chance, crossed 1, meaning that chance was possible. (p. 13).

This was Laroche's conclusion:

"Conclusions.. An analysis of existing systematic reviews concerning the risk of cancer or cancer mortality in firefighters found that the incidence of rectal cancer, prostate cancer, bladder cancer, testicular cancer, mesothelioma and malignant melanoma are consistently reported as significantly higher in this population compared to the general population. The results of SRs also indicate that death rates from rectal cancer and non-Hodgkin's lymphoma are higher among firefighters. *However, caution should be exercised in interpreting these results due to the*

low methodological quality of the SRs reviewed. It is also not possible to generalize these results to all firefighters since the original studies focused on cancer risk among male firefighters. More studies are needed to determine the cancer risk among female firefighters. (p. 17). Italics mine. Laroche did not address female cancers.

Therefore, the data presented by Laroche, though interesting and suggestive, were not of high quality and were not definitive in reference to bladder cancer, but rather were hypothesis-generating, meaning further research is indicated.

In the report by Jalilian, H., Ziaei, M., Weiderpass, E., Rueegg, C.S., Khosravi, Y. and Kjaerheim, K. (2019), Cancer incidence and mortality among firefighters. Int. J. Cancer, 145: 2639-2646. https://doi.org/10.1002/ijc.32199, as had Laroche, Jalilian found, "There was no overall increased risk for all cancers among firefighters. Overall, heterogeneity was statistically significant among all cancers as well as for 11 cancer sites." (p. 2642). For bladder cancer a slight increase in risk of diagnosis, but not definitely of death, was found. Unfortunately, the studies included in this meta-analysis ranged from 1950-2014, including a time when tobacco smoking was very common, and also 59% of the reports included were not from the USA, important in that tobacco use was, and still is, much more common in many countries of the world, including highly developed countries. Female cancers were not addressed.

Therefore the data presented by Jalilian, while concerning for increased risk of bladder cancer in firefighters, may not be applicable to the United States and to current time.

Background:

It may be helpful to provide a discussion of what are called systemic reviews and meta-analyses. An ideal scientific study would compare equally matched groups, one group exposed to the agent or situation of concern, and the other alike in every way except that exposure/situation. This second group is called the control group. Ideally, the time period over which the agent or situation takes place is the same in the control and the study population. Those who are in each group ideally will be chosen by a method without bias, not by a non-random method. Also, ideally, neither the agent or situation, nor the measured outcome will be known to any of the participants nor the researchers, which is referred to as double-blind. Whenever possible, a sham or placebo will be used so that all participants receive a treatment or intervention so they cannot easily guess into which group they were placed. Finally, the best data are collected when research is prospective, meaning collected from the time when the research begins, in contrast to retrospective, meaning collected from information already available. In sum, prospective randomized double-blinded placebo-controlled studies are the ideal. Animal studies can often meet these "rules", however human studies can as well, and these kinds of studies are common in medical research, whether to assess cancer therapies, blood pressure medications, or heart pacemakers.

Examples of studies of which the reader might be aware are sham versus actual knee surgery, showing that in some situations surgery was not helpful; use of steroids for fibromyalgia, which was shown not to be helpful; and use of "old" inexpensive medications for high blood pressure rather than some of the newer medications available. The FDA recently stopped the use of certain monoclonal antibodies for the new Omni variant because research showed these did not help with that variant.

Obviously, these ideal research conditions cannot always be met. Therefore researchers use a variety of ways to try to create situations which as closely as possible meet these goals. One example is to seek out controls who, as best as can be, match the subjects. The use of the New York City age-matched population to try to understand risk to those involved in the 9-11 attacks is an example. Comparison of firefighters' medical diagnoses with age and sex matched community members is another example.

An important principle is what is called sample size. If one tosses a coin, the chance of heads versus tails is 50%, or 1 chance in 2. Everyone will agree that the result is due to chance. However, when there are a large number of events, how does one know if a difference is due to chance, due to something else one didn't even think of, or actually real? In fact, this is a very important, and very tricky question. For example, as the world watches science "in action" trying to know what is real about COVID – what caused it, how it spread, how to protect ourselves from it, if vaccines work, if vaccines are safe, etc. etc. we are watching scientific methods at work, in real time. And, please notice, opinions change as often as new data help guide the scientists. The public feels confusion, however scientists understand that this is normal for any advance – one has ideas, one has information, and of utmost importance, one adjusts one's understanding as new information is available. We no longer think, for example, that asbestos is a great insulator in our houses, or that fiber protects us from colon cancer, but we do believe that seat belts and speed limits save lives, and that vaccinations have nearly eliminated smallpox.

Another principle is the quality of the data or information. For example, if medical diagnoses are not accurately recorded, and those diagnoses are not thoroughly transferred to data bases of firefighters (or any other group such as expectant mothers), conclusions are going to be faulty. If care is not taken when including people in research studies or registries, the information may be incomplete, and thus the conclusions faulty. If there is something about the people being studied that might affect the outcome, has that been taken into consideration – for example, does socio-economic status or education make any difference in the scientific question being asked? – There is good reason to believe that those factors are important in life expectancy, for example. If medical science had not advanced in accuracy of diagnosis in an older study, versus more modern techniques, diagnoses might be missed, or might be "lumped together" making the conclusions faulty.

If one thinks about firefighters, for example, if it is not recorded how much of their time is spend in contact with fire, in contrast to other non-exposure tasks; if it is not recorded what

sort of equipment they had and what were the regulations in regard to use of that equipment – think of fire marshals and of those digging the trenches ahead of the firefighters in wildfires; if use of tobacco by the firefighters is not recorded; if the exposure times are not documented in terms of calendar, which is a surrogate marker (a way to get to information that might not be available) for safety measures; and if other important data are not available, the conclusions are more likely to be faulty. Data from other countries are not necessarily applicable to the USA, because of many factors including different numbers and types of fires, use of volunteer firefighters, age and sex of firefighters, etc.

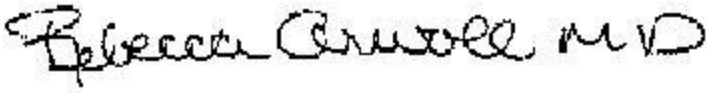
Keeping in mind these kinds of challenges to finding "truth", a technique has been increasingly used called meta-analysis. A meta-analysis is a compilation of data from "all relevant trials addressing an explicit and relevant clinical question." (Lyman) The data come from what is called aggregate patient data, meaning all the numbers from what are considered relevant studies are added together, aggregated. Use of aggregate patient data is in contrast to published reports from individual patient data, meaning the report is not a grouping but reports on the individuals who were in that particular study. Because a meta-analysis can give information about a very large number of people, there is a greater possibility that the results will not be due to chance. However there is a very large caveat – that is what is loosely said in the computer world: "GIGO" or garbage in-garbage out. If the studies being included in a meta-analysis are not well done, and are not relevant to each other, the results will be, using this slang, garbage. If on the other hand, each study included was well done, and all studies used were relevant to each other, the meta-analysis can be very helpful.

I would refer the interested reader to a (relatively) accessible overview of statistics in medical research, noting that essentially all medical researchers defer to expert statisticians before beginning research, in analysis during research, and before publishing. Please consider Krousel-Wood, M.D., MSPH, for a thorough overview, written for Tulane University.

A cautionary note to emphasize how meta-analysis can lead one astray is provided by Esterhuizen, summarized in this introduction: "Meta-analysis, a statistical combination of results of several trials to produce a summary effect, has been subject to criticism in the past, mainly for the reasons of poor quality of included studies, heterogeneity between studies meta-analyzed and failing to address publication bias. These limitations can cause the results to be misleading, *which is important if policy and practice decisions are based on systematic reviews and meta- analyses*. We elaborate on these limitations and illustrate them with examples from the nephrology literature. Finally, we present some potential solutions, notably, education in meta-analysis for evidence producers and consumers as well as the use of individual patient data for meta-analyses." The italics are mine.

The interested reader might look at The Cochrane Collaboration https://www.cochrane.org/, a source which was created to aid international researchers to improve the quality of medical data and decisions.

Respectfully submitted,



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