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Expert Opinion of Suresh H. Moolgavkar, M.D., Ph.D.

In response to the Rejoinder Opinion of Harlee Strauss, Ph.D., and the Opinion of Philippe Grandjean, M.D.

In the matter of an arbitration under the rules of the United Nations Commission on International Trade Law

Chevron Corporation and Texaco Petroleum Company vs. the Republic of Ecuador, PCA Case No. 2009-23

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Purpose of Report

I have been asked to review and respond to the following opinions in the matter of an arbitration under the rules of the United Nations Commission on International Trade Law involving *Chevron Corporation and Texaco Petroleum Company vs. the Republic of Ecuador*:

- Rejoinder Opinion of Harlee Strauss, Ph.D., Regarding Human Health Risks, Health Impacts, and Drinking Water Contamination Caused by Crude Oil Contamination in the Former Petroecuador-Texaco Concession, Oriente Region, Ecuador, December 16, 2013 ("Strauss Rejoinder Opinion");

- Opinion of Philippe Grandjean, M.D., November 22, 2013 ("Grandjean Opinion").

Specifically, I have been asked to address the questions of whether the Strauss Rejoinder Opinion and Grandjean Opinion are scientifically sound as they pertain to epidemiologic principles, and whether they establish that adverse human health outcomes resulted from TexPet's oil exploration and production activities in the Concession Area.

Executive Summary

Based on my review of the Strauss Rejoinder Opinion, the Grandjean Opinion, and the available epidemiologic evidence on the human health impacts of oil exploration and production activities on residents of surrounding communities, my opinion is as follows:

- Neither Dr. Strauss nor Dr. Grandjean provides any evidence or a valid scientific basis for the assertion of adverse human health outcomes from TexPet's oil exploration and production activities in the Concession Area.

My opinions expressed in my Expert Opinion of May 31, 2013 ("Moolgavkar Opinion"), have not changed.

My background and qualifications are summarized in the Moolgavkar Opinion. My opinions expressed in the present report are made to a reasonable degree of scientific certainty based on the information available to me to date. I reserve the right to supplement this report and to expand or modify my opinions based on my review of additional material as it becomes available.

Bases for My Opinion

Risk assessment versus epidemiologic research

As expressed in the Moolgavkar Opinion (p.20), a risk assessment—even if quantitative—is not a substitute for a properly conducted epidemiologic study. A quantitative risk assessment is based on highly conservative assumptions, not on observed risk at low levels of exposure. A risk assessment evaluates what *might* happen under highly conservative assumptions and under possible exposure circumstances in a given setting. Therefore, even if a quantitative risk assessment arrives at a non-zero estimate of risk,[1] it does not imply that an actual risk exists. By contrast, epidemiologic studies evaluate what actually *did* happen and, therefore, are necessary to reach a conclusion that an exposure resulted in adverse health outcomes.

Use of the Bradford Hill guidelines

On pp.38–39 of the Strauss Rejoinder Opinion, Dr. Strauss cites the Bradford Hill guidelines (Hill 1965) out of context and in a scientifically inappropriate manner. As stated in the Moolgavkar Opinion (p.19), where I referred to the failure of the Judgment and Dr. Strauss to use these or comparable guidelines as a basis for consideration of causality, the Bradford Hill guidelines are intended to be used to evaluate whether an observed *statistically significant* exposure-disease association can reasonably be interpreted as causal.[2] Although Sir Austin Bradford Hill (1965) also notes that formal tests of significance cannot directly answer questions of causality,[3] he clearly indicates that these guidelines cannot meaningfully be applied to null associations. In this matter, Dr. Strauss and others have presented no scientifically reliable evidence of significant exposure-disease associations to which the Bradford Hill guidelines can be applied.

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1 Quantitative risk assessments for cancer typically make the *assumption* that the dose-response relationship between exposure to a putative carcinogenic agent and the cancer endpoint is monotone increasing and that there is no threshold. These are assumptions not empirical findings based on actual data. Therefore, if the concentration of a putative carcinogenic agent is vanishingly small, but greater than zero, a quantitative risk assessment will always yield a positive risk. For example, a quantitative risk assessment for a single chest X-ray will yield a small, but non-zero, increased risk of lung cancer. This does not mean, of course, that there is any increased risk of lung cancer associated with a single chest X-ray.

2 From Hill (1965): "…[W]e have this situation. Our observations reveal an association between two variables, perfectly clear-cut and *beyond what we would care to attribute to the play of chance*. What aspects of that association should we especially consider before deciding that the most likely interpretation of it is causation?" [emphasis added].

3 From Hill (1965): "No formal tests of significance can answer those questions. Such tests can, and should, remind us of the effects that the play of chance can create, and they will instruct us in the likely magnitude of those effects. Beyond that they contribute nothing to the 'proof' of our hypothesis."

In citing the Bradford Hill guidelines, Dr. Strauss points to the biological plausibility of the relationship between benzo(a)pyrene and cancer. While I do not debate that exposure to benzo(a)pyrene under appropriate circumstances and at appropriate levels of exposure increases the risk of human cancer, Dr. Strauss and others have failed to establish that residents of the Concession Area were exposed to benzo(a)pyrene at a dose sufficient to cause cancer in humans. In fact, our epidemiologic study in the Concession Area (Moolgavkar et al. 2014) shows that there is no increase in cancer mortality risk in the oil-producing areas.

Cancer risk factors and lack of a cancer excess

Dr. Strauss does not dispute the fact that human papillomavirus is the most important cause of cervical cancer, nor that *Helicobacter pylori* is an important cause of stomach cancer (p.42 of Strauss Rejoinder Opinion). When attempting to identify novel risk factors, not accounting for other major risk factors is a fundamental flaw in any epidemiologic study. Uncontrolled confounding by major risk factors can completely invalidate any estimated exposure-disease association, including those reported by Drs. Hurtig, San Sebastián, and colleagues (San Sebastián et al. 2001a, b, Hurtig and San Sebastián 2002a, b, c, San Sebastián et al. 2002, Hurtig and San Sebastián 2004, San Sebastián and Hurtig 2004).

Dr. Strauss's hypothesis (p.42 of Strauss Rejoinder Opinion) that exposure to petroleum or its components might have caused immune suppression that might in turn have increased susceptibility to infection-associated cancers is purely speculative. An increased incidence of immune suppression has not been documented among residents of the Concession Area, nor is there documented exposure to components of petroleum at doses sufficient to cause immune suppression (which Dr. Strauss does not define as a measurable clinical entity) in humans.

Of note, cervical cancer and stomach cancer risks are only modestly increased in highly immunosuppressed solid organ transplant recipients (standardized incidence ratios ≈ 1–2.5) (Grulich et al. 2007, Engels et al. 2011), indicating that these malignancies are not strongly associated with even severe immune suppression (compared with other malignancies that are increased by more than 20-fold). Thus, more moderate immune suppression, which Dr. Strauss has not demonstrated in residents of the Concession Area, would be expected to have even less of an influence, if any, on disease incidence. In any case, our recent paper (Moolgavkar et al. 2014) shows that there is no increased risk of death from either stomach cancer or cervical cancer in the Concession Area. Moreover, we find no increase in mortality from cancers, such as the lymphomas, known to be strongly associated with immune deficiency. Thus, Dr. Strauss's speculation that exposure to petroleum products might have resulted in immune suppression is totally without merit.

Evaluating whether certain exposures could have caused an excess of certain diseases is irrelevant if no disease excess has been documented. No excess of cancer or other diseases has reliably been documented in the Concession Area population; on the contrary, our research has documented no significant excess of mortality from any cancer (Moolgavkar et al. 2014) or any natural non-cancer cause of death that might plausibly be caused by exposure to petroleum or its components (manuscript in preparation) in oil-producing versus non-oil-producing areas in the Oriente.

Potential for information bias

Dr. Strauss states that "contrary to the opinion offered by Dr. Moolgavkar, medical personnel, not individuals recalling symptoms at a later time and subject to possible recall bias, describe skin rashes to be due to exposure to oil in oil spill cleanup workers" (p.44 of Strauss Rejoinder Opinion). Dr. Strauss is incorrect; information reported by medical personnel is certainly susceptible to information bias. Indeed, the risk of differential ascertainment of health outcomes by medical personnel due to knowledge of patients' exposure status is one of the primary reasons why randomized clinical trials are double-blinded, so that neither study participants *nor the medical personnel conducting the study* can report or record health outcomes unequally between treatment groups, thereby resulting in biased results. Dr. Strauss also ignores the fact that the exposures encountered by oil-spill clean-up workers are not known to be comparable to those experienced by Concession Area residents.

More germane to this matter, on p.13 of the Moolgavkar Opinion, I stated that the results of the study by Dr. San Sebastián et al. (2001b) based in the Oriente region were susceptible to recall bias because they were based on self-reported symptoms. This limitation was acknowledged by the authors themselves.[4]

[4] From San Sebastián et al. (2001): "También puede haber un sesgo en la recordación de los síntomas por parte de las participantes, especialmente al abarcar los 12 meses anteriores ... Por otro lado, la falta de registros médicos y la dificultad de verificar ciertas quejas, como el dolor de cabeza o de garganta, el cansancio, etc., podrían afectar a la validez de los resultados. También debe tenerse en cuenta el sesgo del entrevistador, ya que los investigadores eran conscientes de la exposición a que habían sido sujetas las comunidades. Otra consideración es el sesgo de información, por el cual las personas que creen estar expuestas pueden exagerar la intensidad de los síntomas. Para disminuir este sesgo, en otros estudios se hacen ajustes por el aumento de ansiedad o la creencia de que la exposición podría afectar a su salud (10, 34). En nuestro estudio, no fue posible seguir esa práctica debido al largo período de exposición al petróleo de las comunidades participantes y la creencia entre los habitantes de esas comunidades de que el petróleo estaba desmejorando [*sic*] su salud (comunicación personal)."

English translation: "It could also be a bias in the recall of the symptoms by the participants, especially within the 12 previous months … On the other hand, the lack of medical records and the difficulty to verify certain claims, such as headache or sore throat, fatigue, etc., could affect the validity of the results. The bias of the interviewer should also be taken into account, since the investigators were aware of the exposure the communities had been subject to. Another consideration is the information bias, through which people who believe to be exposed may exaggerate the intensity of their symptoms. To diminish this bias, other studies make adjustments by the increase of anxiety or the belief that the exposure may affect their health (references

Contrary to Dr. Strauss's suggestion that "regular practices" are not subject to recall bias (p.9 of Strauss Rejoinder Opinion), any past exposure that is self-reported, regardless of its frequency, is susceptible to misclassification and, if reported after disease occurrence, susceptible to recall bias (i.e., differential misclassification) due to systematically unequal reporting between diseased and non-diseased persons.

More importantly, Dr. Beristain et al. (2009) did not compare the frequency of dead fish consumption between diseased and non-diseased persons, and therefore did not estimate the association between dead fish consumption and disease risk. Dr. Beristain et al. (2009) also did not evaluate the frequency of dead fish consumption in a comparable area without oil exploration and production activities. Consequently, this study provides no scientific evidence that consumption of dead fish was increased due to TexPet's oil-related activities, nor that such consumption affected the incidence of any disease in Concession Area residents.

Timing of pregnancies

Dr. Strauss suggests that the implausible finding of Dr. San Sebastián et al. (2002) that petroleum exposure was more strongly associated with spontaneous abortions in earlier pregnancies than later ones might be due to "higher exposure to fresh oil during earlier time periods, i.e., during earlier pregnancies" (pp. 50–51 of Strauss Rejoinder Opinion). However, Dr. San Sebastián et al. (2002) did not analyze pregnancies by year, which would have been highly variable in a group of women aged 17–45 years. Thus, there is no evidence to support Dr. Strauss's conjecture that the apparent association with spontaneous abortions was stronger for pregnancies that occurred during TexPet operations than during Petroecuador operations.

Moolgavkar et al. (2014) versus Hurtig and San Sebastián (2002b)

Dr. Strauss relies on the opinion of Dr. Grandjean regarding epidemiological issues (p.5 of Strauss Rejoinder Opinion).

Dr. Grandjean opines that although "solid scientific proof" of an adverse health impact of TexPet's oil exploration and production activities is not available and indeed cannot be expected to be obtained (p.2 of Grandjean Opinion), it is plausible that such an impact occurred. However, Dr. Grandjean acknowledges that there is no solid scientific evidence to support his

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10, 34). It was not possible to follow that practice in our study due to the long period of oil exposure in the participant communities and the belief among the inhabitants of those communities that the oil was deteriorating their health (personal communication)."

position; in fact, based on the findings described in our now-published study (Moolgavkar et al. 2014), the evidence is directly contrary to this opinion.

Dr. Grandjean opines that our classification of cantons with versus without oil exploration and production activities probably led to mixing of the exposure groups, whereas the classification used by Drs. Hurtig and San Sebastián (2002b) was more appropriate. However, he offers no scientific basis for this opinion. Drs. Hurtig and San Sebastián themselves provided no data to support their classification, whereas we provided quantitative data on oil wells and oil production to support ours. The cumulative number of barrels of oil produced as of 1990 in cantons that we classified as "active" in oil exploration and production ranged from 9,846,000 to 409,845,000, with a median of 141,668,000. Twelve of the 13 cantons that we classified as "inactive" produced zero barrels of oil as of 1990, and the 13th canton produced only 422,000 barrels. Thus, there are stark differences in oil production activity between these groups. Of note, Drs. Hurtig and San Sebastián (2002b) classified the canton of Cascales as "non-exposed" despite the fact that it had produced 9,846,000 barrels of oil as of 1990, and they apparently excluded the cantons of Putumayo and Cuyabeno, which had produced 18,725,000 and 20,180,000 barrels of oil, respectively, as of 1990. Moreover, as noted in our paper (Moolgavkar et al. 2014), we found no significant associations with cancer mortality when we classified cantons according to the system used by Drs. Hurtig and San Sebastián (2002b).

Non-differential misclassification

Dr. Grandjean states that misclassification resulting from residential migration over time and from the crude exposure categorization will "dilute any association with adverse outcomes" (p.3 of Grandjean Opinion), and that "studies on average are biased toward the null, thus leading to an underestimation of the risk" (p.9 of Grandjean Opinion). These statements are not scientifically sound.

First, Dr. Grandjean has no evidence that residential migration over time will lead to attenuated estimates of association. If persons at low risk of cancer tended to migrate to areas without oil exploration and production activity and/or if persons at high risk of cancer (or dying from cancer) tended to migrate to areas with such activity, then estimates of association would be biased upward. For example, if more health care services were available in areas with oil-related activity, then persons might relocate to such areas for evaluation of symptoms prior to cancer diagnosis or to receive cancer treatment prior to death. There is no evidence that residential migration is random (non-differential) with respect to exposure and risk of cancer incidence or mortality.

Second, Dr. Grandjean is incorrect that random (non-differential) misclassification leads to underestimation of an association. As noted in the Moolgavkar Opinion (p.21), non-differential

misclassification does not necessarily result in bias toward the null; other conditions must be present for bias to be in that direction (Thomas 1995, Weinberg et al. 1995, Jurek et al. 2005). Furthermore, even if all conditions are met and the likely direction of bias is toward the null, any given estimate can still be biased away from the null.

Third, the majority of relative risk estimates reported in Moolgavkar et al. (2014) are lower than 1.0. For these estimates, bias toward the null leads toward underestimation of an inverse association. That is, if Dr. Grandjean is correct that residential migration over time and exposure misclassification led to attenuation of these estimates, then the true relative risks would have been even lower, i.e., in the direction of a protective association.

Potential for differential outcome misclassification

Dr. Grandjean does not acknowledge that unequal access to the Quito health care system could have resulted in differential outcome misclassification in the studies by Drs. Hurtig and San Sebastián (Hurtig and San Sebastián 2002a, b, c, 2004, San Sebastián and Hurtig 2004), nor does he acknowledge that underestimation of population growth would have led to an upward bias in the relative risks estimated in those studies.

As explained in the Moolgavkar Opinion (p.15), only cancer cases diagnosed in Quito were included in the analyses by Drs. Hurtig and San Sebastián. If persons living in areas with active oil exploration and production had better access to roads and means of transportation, and were therefore more likely to be able to travel to Quito for cancer diagnosis, compared with persons living in non-oil-producing areas, then observed relative risks would have been biased upward.

In addition, as explained in the Moolgavkar Opinion (p.10), Drs. Hurtig and San Sebastián used outdated estimates of the size of the populations at risk in their studies. Because population growth over time in oil-producing cantons was substantially greater in oil-producing than non-oil-producing cantons, they would have preferentially overestimated cancer incidence rates in oil-producing cantons, thereby leading to overestimated relative risks. These important limitations were ignored by Dr. Grandjean as plausible explanations for the observed cancer excesses reported by Drs. Hurtig and San Sebastián.

Interpretation of 95% confidence limits

Dr. Grandjean suggests that the upper limit of the 95% confidence interval should be interpreted as reflecting “the highest extent of excess risk that would be in accordance with the findings” (p.10 of Grandjean Opinion). Such a scientifically unjustifiable approach would place undue emphasis on results based on small sample sizes. That is, the smaller the sample size, the less

statistically stable the result and the higher the upper confidence limit, such that virtually all exposures would be classified as highly hazardous when analyzed in small datasets, regardless of the true hazard of the exposure. For example, in a small dataset, a harmless exposure might yield a relative risk of 1.0 with a 95% confidence interval from 0.1 to 1,000. It would be absurd to rely on the relative risk of 1,000 generated by such limited data.

False positive versus false negative results and absence of evidence

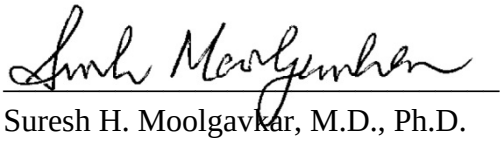
Dr. Grandjean highlights examples of public health problems caused by false negative results, i.e., "ignoring true hazards" (pp.11–12 of Grandjean Opinion). He also suggests that claims of false positive results are exaggerated (p.12 of Grandjean Opinion). Abundant counter-examples of false positive results exist, such as Bendectin and silicone breast implants, as discussed in numerous scientific papers (for example, Ioannidis (2005), Boffetta et al. (2008), Morfeld (2009), Ioannidis (2011), Ioannidis et al. (2011), Prinz et al. (2011), Begley and Ellis (2012)) and in the Moolgavkar Opinion (p.30)). Neither set of examples is directly relevant to the present matter.

Dr. Grandjean states that "absence of evidence is not evidence of absence" (p.11 of Grandjean Opinion), but he goes even further to imply that in this case, it is evidence of presence. As acknowledged by Dr. Grandjean, there is no reliable scientific evidence of the presence of an adverse health impact attributable to oil exploration and production activities in the Oriente region.

Conclusions

In conclusion, the Strauss Rejoinder Opinion and the Grandjean Opinion do not alter my original conclusion (p.23 of Moolgavkar Opinion) that the available epidemiologic evidence does not support even a statistical, let alone a causal, association between oil exploration and production activities and cancer or other adverse human health outcomes in residents of surrounding communities, either in general or specifically in the TexPet Concession Area.

I affirm that the opinions stated in this report are a true and accurate expression of my genuine beliefs.



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