

BZ IOM review: API input to CONCAWE

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Date:

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Ken and Shan,

Jan Urbanus has asked the API BZ taskforce for response/reply/recommendations re: the IOM data consistency report. While I'm the default contact in the BZTF on this project, I also have a stake in it, so I believe the best strategy would be to get a note to CONCAWE that reflects what the three of us can agree on. While I know that both of you have worked with Louis Bloemen on this previously, Dow is not part of API, so I don't think it's necessary to get his views as well. I feel a bit awkward 'barging in' like this, but I do think API should have a voice in this since they are a funder. I have read Shan's input to CONCAWE, Ken's input to CONCAWE, and Ken's input to Chevron's BTF rep, (Russ White). You probably don't know my input, so let me describe it, and from there, we can probably arrive at a least common denominator.

First, from an XOM management perspective, there are some constraints in terms of costs that are real. If the project is too costly, (e.g. if it asks for funds beyond what the BTF (and tentatively, CONCAWE and CPPI) has budgeted, there will be less support for moving forward at least from our company's perspective. I believe the TF has an extra 70K budgeted this year, and 100K in the next two years, for 270K. CONCAWE, I believe has spent its 05 funds, but has contributed on par with API in the past (say, 200K for 06 and 07), while CPPI has contributed about 10-20% (say 30K total) of that. The Energy Institute (formerly IP) funding was also a minimal amount, but I'm not sure their funding can be depended upon, since BP has a big voice there, and my read is that they are not supportive of moving forward. So, it looks like costs have to be kept at around 500K, at least for XOM to be supportive (this is all tentative, and we have meetings with the company to flesh this out further).

500K may sound like a lot, but we need to involve a lot of people, perhaps up to 13 when you include people who have a stake in HW, IOL, IP, IOM, IRAS, former SAB (I'd love to get Dave Verma to contribute), a hematologist (Larson?), and one or two others. While some may have 'review' rather than 'conduct' duties, it adds up.

While scientifically I would love to use the extended follow-up cases in IOL, IP, and even HW studies, this has some practical downsides. Both of you have said updates would be more beneficial for the IOL study, and I agree, that is where we have the most to gain. And it is certainly possible to do this, but practically it would extend the analysis several, (perhaps up to 18 months) beyond the base case. Records for new leukemia cases and controls need to be: (a) sent to Stat Can, (b) re-matched to their files, (c) sent with identifiers to IOL, (d) sent from IOL to various operating terminals/record storage centers in Canada to locate manual work histories, (e) have work histories abstracted at each site/center, (f) re-code/reduce consistent with the last study, (g) possibly collect new

operations/product info at relevant sites to allow appropriate BE selection and K-factor estimates (if a site/job/era combo was absent from the last study), (h)summarized and sent back to StatCan, (i)anonymized by STat Can and (j)sent to EMBSI. While some rationalization of exposure could be proceeding simultaneously, including the new cases would likely cost between 200-300K. As is (without the update), IOL contributes 16 leukemia cases, or 12% of the combined total. As Ken points out, its not much, but with 140 cases, I think every case counts, and there's still value in including them. We perhaps should consider updating the IOL and perhaps IP numbers as phase 2.

I agree that some 'exposure rationalization' is needed. There are some straightforward items such as providing more consistent use of k-factors, making sure BE's are comparable, using a common background exposure, etc. I am certain that this can be done on an individual person-by-person basis, I;m not sure why there is some doubt about that. I don't believe creating an 'international exposure database' and developing a model, and tweaking it with expert judgement all over again would be worth the time and effort. In fact, I could argue that some of this would CREATE misclassification. We have a model ($WE = BE * Kw * Kt * Ke * Kp$), and I don't see the logic in re-doing it all over again. What seems to be forgotten in the IOM report, is that exposure estimates were derived individual-by-individual and there are some expected nuances that create different, yet justified, estimates by study (and even within studies). If either of you are interested, I can share the comments I made to IOM, mostly on the IOL study.

I also think there should be some review of the existing leukemia subtype information, so that it is classified in a common way. A review of how the existing information was used, however, and perhaps development of a 'certainty index' for the diagnosis would certainly be feasible. I've talked to two hematologists in the past week about this. Both recommended AGAINST a "panel of hematologists".. it conjures up 'grand rounds' debates and a high likelihood of unproductive tangents. Someone who is used to research (not always in the clinic) is needed..its almost a different skill -- how best to use the existing info.. Due to the tightening of privacy, access to the raw material would be very problematic from the cancer registry viewpoint. It might be more feasible if we were only talking about a few hospitals (almost all routinely keep slides for 25+ years by law, (perhaps fewer years in the UK)). But for 140 cases, we may have to deal with 70 hospitals. Chris Roythorne mentioned waiting for the Shanghai cell type info to emerge. Certainly, the SHS study has great daignostic capabilities -- using the new WHO techniques, cytogenetics, flow, immunohistochemistry markers, etc. You cannot go back and apply that historically, though. The SHS will confirm that cell type distributions in China are very different than in the West (not new), but also somewhat different than what they are perceived to be in China today (e.g. there DO exist CLL's in China!). We know that 95% of what were CLL's in the past would be classified as small B cell lymphomas in the new WHO scheme. This is known, and thus, strictly speaking, the study will (largely) be of two leukemia cell types (AML, CML), which remain the same in the new scheme and two subtypes(ALL, CLL) which are (largely) technically lymphomas in the new scheme. I'm not sure I see the issue with this, as long as its recognized. Remember that there are a fair number of diagnoses that are very straightforward and easy. Rich Irons says that even using ONLY histology (which was the only thing in place back in the 60's + early 70's), you're right something like 90% of the time. This improved into the 80's and 90's.

I also think no matter what improvements in exposure estimates are made, there will be some that are more uncertain than others. That is where I see sensitivity analyses coming in. Recently, in a pooled analysis of radon exposures, Krewski et al. limited the analysis to individuals with more

robust radon readings, and got a stronger dose response. That gives you more confidence in the initial dose-response results. (and vice versa applies, too).

Also, using GAM techniques, I think is a given. I would like to talk to you, Ken, more about this. By the way, the graphical displays in the IOM report, may be flawed... we think there is always a relationship between what is graphed on the x versus y, even for totally random data. Yet, I do like the concept they presented, perhaps it can be tweaked. Agree that categorical schemes can still be used with some sensitivity anal.'s

As far as including DSM, Dow, Monsanto studies, I don't beleive that the data consistency report addressed this, and it shouldn't be mentioned (agree with Shan, but not sure where you are on this, Ken). The exposure estimating in these studies uses a different strategy, more appropriate for larger cohort studies. If the IOM group questioned the consistency of exposure assessment in the IOL, IP, and HW studies, they would probably come back with an answer of "not feasible" if the same standards/logic is used to compare the case control and cohort studies. That being said, I think it would be another interesting project to consider pooling the relatively small cohort studies together.

I also think that there is a 'base case' aspect to pooling the data that should not be overlooked. Some of the things that should be included in the base case -- common measures of intermittency/peak, common measures of lag, etc. Some of the data formatting and resolution issues are not trivial, and just doing a pooled analysis with no improvements has some finite (100-200K?) cost to it.

To summarize, in reviewing both of your comments, I think we can (a) "accept" the IOM report (b) agree that pooling is feasible and justified, (c) seek some degree of exposure rationalization, (d) seek a degree of leukemia subtype rationalization, and (e) perform some sensitivity analyses to quantify uncertainty with respect to exposure and disease classification uncertainty. We still may have issues of 'degree/scope' regarding (c) and (d). We also apparently disagree on the usefulness of updating the IOL, and perhaps the wisdom in including the cohort studies. Please let me know if you think this is a fair summary, and if you have any additional thoughts on including the additional IOL follow-up info.

Sorry for the long note,

Rob

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