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Truth and Meaning in the Determination of Radiogenic Risk

by Douglas J. Crawford-Brown

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Let me start with the assumption that the reader is concerned with determining the risk imposed by human exposure to radiation. These exposures might occur, for instance, in the routine operation of a radiotherapy unit or in some phase of testing a radio-labeled pharmaceutical. The question I want to address concerns the extent to which anyone engaged in the approval of such activities can base his or her opinions and decisions on firmly logical grounds. In other words, in assigning a level of risk to be expected from a given exposure to radiation, when should we feel that past experience dictates an answer and when should we admit that estimates contain significant judgments that might differ among "reasonable" people? While I can offer no final answer to this question, I shall explore the features of such an answer by examining a distinction between "truth" and "meaning" in science.

One method for dealing with problems requiring a great deal of scientific expertise is to seek the opinions of the scientific community. Acting on the basis of estimates provided by a scientific expert involves accepting the best judgments made by people who have carefully examined the past. The idea is that all reasonable people, if only they had the time and training to examine the scientific evidence, would arrive at identical scientific judgments.

Scientists do not, however, come to the same judgments based on past experience. They differ in their interpretations, leaving an IRB with the problem of determining which judgment the members themselves would have arrived at if they had been able to deal directly with the evidence. I intend to explore this problem in this article and to come to some understanding of why scientists differ in their judgments. I intend also to develop a set of ideas, arising from epistemology, which the layperson can use in examining these differences. I hope to show that risk estimates put forth by individual scientists involve selecting one possible interpretation from a rather large group of perfectly valid interpretations of experience. This process of selection should not be expected to be the same in all "reasonable" people, for it will depend on a judgment of the possibility, and consequences, of incorrect selection. While weighing the risks and benefits of an action will probably remain a purely personal judgment, it is currently possible to deal explicitly with the problem of competing estimates of those risks.

The example I'll employ derives from my recent work in developing age-dependent metabolic, dosimetric, and radiobiological models.[1,2,3,4,5] Such models are intended to predict the uptake, disposition, and biological effects following exposure to radiation or radioactivity. (Yes, they are different; radiation refers to the entity that actually causes damage and radioactivity refers to the property of an atom that gives rise to that radiation.)

First, a few technical descriptions. *Metabolic models* are mathematical descriptions of the amount of a radionuclide (radioactive atoms) expected to be found in an organ or tissue at some time after entering the body. *Dosimetric models* describe the relation between the physical location of the radionuclide at the time it undergoes decay and the points at which this radiation is absorbed by the body. Finally, *radiobiological models* provide estimates of the biological effect expected from a specified level of absorbed radiation.

Each of these models must be specified before the risk expected from exposure to radioactivity can be determined. Conversely, any scientific estimate of radiogenic risk employs such models, with the confidence in predictions being in rough proportion to the confidence in the underlying models and empirical data. Let me start by examining the general role of models in making decisions and return at the end to an assessment of the validity and im-

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pact of current models of the risk imposed upon various age groups by intake of a radionuclide.

Rationality and Choice

What do we mean when we say that a decision is arrived at rationally and (for I think the two are related) scientifically? There is a clear reference to some relationship between strongly held beliefs and the final decision. Rationality is a process of ensuring that each of those beliefs plays some role in tempering that decision. It provides a framework for discussion, serving both to focus attention on crucial beliefs and to determine the importance of all past experience in light of future goals. In short, it gives a coherent set of statements toward which we can direct our logical and emotive faculties.

I have in mind the syllogism as a classical, albeit simplistic, example of rationality or rational thought. Syllogistic reasoning starts with a few "givens" of experience, e.g., "In the past, humans injected with radium incorporate it into their bones; John is human"—and proceeds to infer something new—"If injected, John's bones will incorporate radium." The strength of the inference is determined by the extent to which the "givens" are known to be true and the force of our belief about the relation between past experience and the present. Weakness within any rational thought creeps in whenever these "givens" are questionably true, or when they are not clearly applicable to the task at hand. In other words, through rational discussion the facts (or "truths") of past experience impart meaning to statements about the future.

I've chosen this particular example because it represents some sort of ideal toward which all definitions of rationality strive. Each "given," or a priori condition or belief, is verifiable empirically by all humans and hardly subject to reasonable contention. In addition, I believe that the simple logical principles employed (namely, that the physical future is governed by the same laws as the past, and that the member of a group is subject to any physicial law controlling the other members of that same group) to be strongly held by all "reasonable" people.

While the final inference cannot be proven true, in the deepest sense of the term "a priori" (that is, prior to injecting John), it nevertheless seems clear that past experience makes the inference highly likely. In other words, past experience imparts strong logical meaning to the inference and one should feel justified in acting on the basis of the inference. Of equal importance, however, is the observation that these same experiences do not appear to make any other inferences meaningful. Their existence, for example, would not serve to give meaning to the statement, "John will fail to incorporate radium"—unless, of course, I introduce the premise that the opposite of the past sometimes occurs. As we shall see, this quality of singular implied meaning is not typical of bodies of experience employed in arriving at scientific estimates of risk.

In general, the problems faced by members of an IRB differ from the above example in two fundamental respects. In the first place, the necessary inferences are not of an "either/or" nature, but rather are ones of degree. We usually take as a given that an experiment involving radiation exposure will impose some risk on an individual (unless there is a threshold of some sort). We would like to know the level of that risk, so that we can compare it with the benefits. This implies a need to determine, for example, the quantitative extent to which injected radium will incorporate into John's bones, and not just whether it will enter. This requirement becomes a significant problem when seen in light of the second difference, namely, that new experiments are being performed precisely because past experience does not dictate the outcome. Instead, this experience exists in bits and pieces, which are suggestive of the outcome of the new experiments, as long as we are willing to make some assumptions.

These assumptions comprise the models on which much of science is based. Models provide a framework of rationality by which we can relate past experiences to future expectations. Without them, we can't determine the effect of any important differences that might exist between past experience and a proposed experiment. To be more precise, we might be able to guess the direction in which the effect will move but not the extent of the movement.

For example, suppose we want to infer the risk imposed on John by injecting a given amount of radium, say, one gram. Imagine further that past experience has been restricted to studies in which ten grams of radium have been injected, and that measured risk in this hypothetical situation was found to be a one in ten chance of death. One model might consist of the assumption that the risk is in direct proportion to the amount injected. We could then develop the following syllogism:

1. Persons injected with ten grams of radium have a risk of one in ten of death.
2. Risk is proportional to the amoun of injected radium.
3. Therefore, if one gram of radium is injected, the risk is one in a hundred (one-tenth of what it would be were 10 grams injected).
4. John has been injected with one gram of radium.
5. Therefore, the risk of death to John is one in a hundred.

This syllogism, then, is precisely the kind of reasoning we feel lies at the base of scientific statements. The critical step here occurred in line 2, where the model was interposed between past experience and the inference. If another model had been inserted—if we assumed, for example, the risk to be independent of the amount of injected radium—then the inference would change. The disquieting suspicion is that many lines of rational thought might be possible if we should find ourselves in the uncomfortable position of having several plausible models. Each model ensures that the assignment of risk will be a rational process, yet each process leads to a different estimate of that risk. It is not enough, then, to insist on rationality in the simple form offered by the original syllogism. We must have a rational basis for choosing between or combining competing lines of reasoning, of assigning some higher level of meaning to each rational scheme. That brings us, at long last, to science and the role it plays in rational thought.

The state of science at any moment encompasses the beliefs of all competent practicing scientists. If, at a given moment, I choose to answer a question that requires scientific knowledge, then I will find individual scientists who disagree about the nature of that knowledge. How can this be true if, as we all learned from Sir Karl Popper,[6] science continuously pushes forward with a single, growing truth? Are some of the scientists simply out of step with this truth, choosing for personal reasons to ignore the rules of logic and bodies of past experience? Wouldn't these dissenters, when struck with pangs of guilt, see the light and adopt the official singular "truth"? Thomas Kuhn, in *The Structure of Scientific Revolutions*,[7] answers these questions with a resounding "no," and I agree with him. The reason is found precisely in the insistence on rationality in science and the resulting need for models of reality.

Theories, and their associated models, are crucial to the progress of scientific knowledge. Without them the

scientist is faced with a jumble of experiences, some relevant and some irrelevant. This disordered body of experience is by no means logically connected to inferences. Theories and models bring some partial order, albeit an artificial one, to this chaos, serving to explain each experience in terms that encompass all similar experiences. In fact, they define what we mean by "similar" and "relevant."

Without these theories and models, scientists have no way to logically compare inferences about the future, no language for discussing why particular experiences are important and why they suggest any given inference. Further, theories and models provide a means for assigning a quantitative and qualitative degree of validity to that inference, with the strongest support going to inferences arising from the model best able to provide an explanation of past experience.

Models are necessary constructions for rational thought and scientific debate. Because of the fragmentary nature of scientific experience, consisting of isolated experiments, one often is faced with several competing and perfectly logical models (Kuhn uses the term "paradigm"). Recall the dot drawings over which we all labored as children, carefully connecting the numbered dots to create a picture. Take away the numbers and you can see the plight of the scientist. We find one pattern among the dots just in time to be confronted by an alternative pattern. It is not clear which is the "correct" pattern. The number of such patterns may not be infinite and, if we are lucky, they may share some general features. If this is the case, we may not care which pattern we choose as a basis for action, because each may function heuristically like the others. This often happens with scientific models, each leading to roughly the same set of inferences about the future. In any event, increasing the number of dots or experiences may narrow the range of reasonable pictures until only one remains. Unfortunately, this is rarely the outcome, except in certain realms of fundamental physics.

Differences between models do exist, however, and they lead to quantitative differences in inferences and extrapolations (such as the risk of injecting John, in our earlier example, with one gram of radium). Individual scientists may well choose to work within a single model, recognizing that choosing the "wrong" model may still serve as a guide to the truth, encouraging the right questions to be posed and answers sought. This choice often is based on the "most likely" model, the one showing the best fit (concordance) between its predictions and past experience. Sometimes there is general scientific agreement on which model is "most likely" to be correct. This convergence of opinion onto a "most likely" model is accomplished by the scientific community through personal contact, conferences, and the review of journal articles and experimental protocols.

Complete agreement within the community usually does not hold, however, due to differences of opinion over which experiments are to be counted as the "reality" that a model must fit. One model often works best in one realm of experience but must yield to another model in a different realm. It is not always clear which realm is most relevant to the task at hand. In addition, experimental measurements are to some degree imprecise, and the observed quantities bounce about during and between experiments. This leads to statistical problems that demand that each model continuously predict answers varying to some extent from past experience.

A given model, then, becomes "likely" in light of past experience, with models differing only in their assumptions and in the degree of this "likelihood." Each model is possibly the "true" one, and the past cannot tell us which it is. All it can dictate is the extent to which any given model ought to be believed. In any event, individual scientists, or the scientific community, still are free to choose a single model (and line of rationality), with the understanding that they will pay the price of choosing incorrectly. I don't believe that those faced with societal decisions (and I include the IRB in this group) can make this assumption.

Therefore rational decisions must include a consideration of all possible lines of rational thought; our ethical responsibilities involve a consideration of the inferences arising from all such lines. The amount of relative consideration given to each estimate of risk will depend on the degree of logical and scientific support, as well as value judgments on the consequence of failure. However, the principle of choice employed will depend on the consequences of an incorrect decision. An incorrect decision in science delays our collective progress toward "truth," and may also mean a loss of prestige for the individual scientist. As a result, scientists tend to justify using the "most likely" model in their research.

This choice is by no means a simple one, however. One does not necessarily act on the basis of a model just because it is "most likely." The strength of the model in explaining past experience and of its relevance to the future experience must also be considered. Where this support is weak, or where other models are equally strong, it is perfectly rational to postpone a decision or to include consideration of competing models. The level of strength required before a single model is chosen as a basis for action is not arrived at logically but is instead a personal judgment. There is no reason for this judgment to be the same in all reasonable people.

Developing plausible models of reality will, with good reason, remain the task of science. Only the scientist perceives the vast body of basic empirical experience from which rational choice must spring. We cannot accept a line of reasoning completely until we've seen the physical evidence on which it, in part, depends. That's why an IRB turns to the scientific expert for assistance. There is good reason to assert, in addition, that science should provide recommendations regarding the degree of support to be accorded any given model. This degree of support may be quantitative, as in the case of statistical measures such as "goodness of fit." An example here would be any attempt to quantify the extent to which a model predicts the existing data. It is the basis for assigning numerical values to estimates of risk, and is backed by a long history of thought and research. The degree of support may be qualitative, recognizing that a scientist often must make judgments based on tacit knowledge derived from experience but irreducible to mathematical terms. Two models might for instance predict equally well the experience and yet one might be based on assumptions that appear unlikely. In this case, the scientist may indeed have some subliminal reason for the judgment, and we would like to include this form of wisdom. On the other hand, this judgment may be no more than a random guess, unsupported by fact.

Models of Radiogenic Risk

Up to this point, we have been looking at the question of risk assessment from a purely theoretical viewpoint. The following discussion will, I hope, provide insight into the effects of models on estimates of radiogenic risk. I shall employ a single example throughout; an attempt to estimate risk imposed on a child by inhalation of a radioactive compound. The example should serve to illustrate the use of all three types of models described earlier

(metabolic, dosimetric, and radiobiological). In addition, it will demonstrate the varying levels at which consideration of uncertainties may enter the use of models. To avoid the temptation of reverting to a highly technical discussion, no specific radionuclide will be assumed.

The dose delivered to the lung by inhaled radioactivity depends on two factors—the amount of a radionuclide deposited in each breath and the length of time it remains in the lungs. A large number of measurements are available on the first factor in adults. Direct experience includes studies using varying particle sizes, breathing patterns, and states of health, each of which affect the amount of deposition. If the subject were an adult with a breathing pattern and state of health similar to the humans in past experience, there would be no need to introduce a model and the reasoning would be the same as in our original syllogism. However, past experience itself is ambiguous; the measurements differ from experiment to experiment, subject to subject, and, ultimately, between separate exposures to the same subject. All that can be said about the deposition in any future experiment is that past experience suggests it will be between such-and-such bounds, with a "most likely" value equal to the average of past experiences. The exact deposition cannot be specified, although various statements about it can be given. It is possible that the deposition in a specific subject will be greater than (or less than) the average. Just how possible this is will depend on the number of times in the past that the average was exceeded. The credence placed in any estimate of deposition can be no greater than the fraction of past instances in which it was observed.

What is the "true" deposition going to be? That is a truth which science cannot claim to know, and yet a statement concerning this deposition is necessary in any rational line of thought on the subject of risk. If 10% of the past measurements of deposition were larger than the average by a factor of 2, we must assume that there is a 10% chance of our present subject receiving twice the estimated (average) deposition. An important point here is that past experience allows us to quantify the uncertainty.

Much less direct experience is available on deposition in children. This deposition can, however, be predicted by developing a mathematical model of the lung that incorporates all known factors likely to influence deposition. These basic physiological, anatomical, and physical factors have been used to develop a model, which in turn predicts well the deposition in adults (within the bounds of variability noted above). Since the model is derived from knowledge gained by extensive experience with more controlled experiments, we assume the model to be sufficiently similar to the "true" model to warrant action on the basis of its predictions. This was supported recently when my own model predictions for various ages were compared to those obtained from another model. This second model, developed by another researcher[8] and starting from different assumptions, yielded results remarkably similar to my own, an outcome more often the exception than the rule, and indicating only the relative simplicity of the problem.

We "feel," therefore, that the models are similar and that acting on the basis of one is essentially the same as acting on the basis of the other. This is what I meant earlier by saying that the two models might be "heuristically" the same. At the same time, it must be recognized that we can't quantify our uncertainty, since there is no direct experience to provide a means of comparison. Both models, of course, require information on lung anatomy for the subject. This specific information rarely is available, but has been measured in other people of similar ages. Once again, these anatomical measurements vary between individuals, and we cannot know which set of measurements applies to the current subject. The best we can do is to look at the effect of using any given measurement in making predictions and compare this to the predictions using another measurement. Each prediction then receives credence (or meaning) according to the chances that our subject has this particular anatomical value. In any event, predictions using simple average values should be accurate to within a factor of 2 or 3 for essentially any subject under controlled experimental conditions.

Radionuclides deposited in the lung can enter the bloodstream, and the following remarks apply both to these radionuclides and to those that are injected directly into the blood. The remarks also apply to the injection of new drugs regardless of whether they are radioactive. The dose delivered to an organ depends on the fraction of the radionuclide that enters the organ and the length of time it remains there. As in the case of the lung deposition, this initial fraction varies widely between individuals and we cannot know, prior to an experiment, what the actual value will be, although past experience suggests the extent to which any given value should occur. Since similar experiences are much less certain in children, it has been necessary to develop a model relating organ size and rate of growth to the age-dependent amount of uptake of a radionuclide. Unlike the case of the lung, however, the conceptual strength of the model is rather weak, since we have no real understanding of the underlying physical and chemical processes. Different models here yield both different results and different feelings of "reasonableness" about the assumptions.

The total length of time a radionuclide remains in an organ may also be determined partially from past experience. This experience is limited, since experimenters usually cannot follow a subject for great lengths of time. In order to determine the risk, however, we need to know the behavior of a radionuclide over longer periods of time (although this is less important for radionuclides that decay quickly). Models are, therefore, necessary to account for the behavior of the radionuclide at times longer than the length of past studies.

Different models can, and do, "fit" the available adult data equally well and yet lead to differences in predicted behavior at longer times. A typical example here would be the use of exponential functions or a power function. Inferences using both approaches, where appropriate, should be developed and considered within a total scheme of rational choice. Such a scheme must also recognize that these functions themselves vary between individuals. Different scientists also use different bodies of data to infer this function, with some preferring the rather extensive "nonhuman" data over the scanty "human" data. In any event, the uncertainty here is intermediate. The models themselves have only moderate conceptual support, but there are enough data to check their behavior at early times after injection.

Similar problems arise in the models for dosimetry and radiobiology, although it should be noted that dosimetric models are usually much more certain than metabolic models. It is rare that the dosimetric model will introduce an error of more than 50%. Radiobiological models, however, show great variability in estimates due to different assumptions about the ways in which radiation causes cancer.

A good example of this is the recent controversy over the National Academy of Sciences BEIR report.[9] The controversy was essentially double-sided,

involving a choice between relative and absolute risk models and between various models for extrapolating risk estimates from studies at high doses to those at low doses. The choice between relative and absolute risk models involves a decision concerning the likelihood that radiation-induced cancer acts in conjunction with "naturally-induced" cancer. There is no way to quantify this likelihood. Each model has its advantages, and regulatory bodies usually look at risk estimates arising from both and then base their decisions on a subjective appraisal of each.

The problem of extrapolation to low doses illustrates the impact of uncertainty on selecting a single inference of risk from among a range of inferences. As in the choice between absolute and relative risk models, choosing a method of extrapolation requires some knowledge of the way in which radiation causes cancer. Unfortunately, this process is not well understood; we typically look for guidance in the "shape" of the dose-risk curve at high doses and hope that this "shape" will continue to be true at low doses. Due to the small number of past exposures to radiation, the data are highly variable, and it is difficult to determine what curve "shape" best approximates past experience.

The best we can do (with honesty) is to determine the extent to which any proposed "shape" explains this experience. We can, then, develop a numerical "measure" of how well any shape fits the data and use this "measure" to compare different shapes. Each shape enters into the process of decision according to its relative ability to explain the results of data at high doses and the extent to which the model assumptions are reasonable in light of current radiobiological knowledge.

An alternative approach to decisions has been used in the past in setting radiation protection standards. In fact, it is probably the approach scientific experts use most often in reporting to an IRB. The approach recognizes the uncertainties involved and chooses a "plausible" model, which will predict the highest risk. This model is the linear extrapolation model and assumes that the risk is directly proportional to the dose. We believe this estimate of risk to be "wrong" in some sense, but feel that it is at least wrong in the "right" direction. In other words, if the estimate should prove to be incorrect, it is very likely that the risk will have been overestimated. This provides a margin of error and, one hopes, the "true" risk will turn out to be much less. (Note that the idea of being wrong in the "right" direction already involves a judgment about which type of decision error is desirable.)

We cannot, however, eliminate the possibility that even this conservative estimate of risk may be too low. In addition, this estimate applies to an average person. If the relative risk model is correct, there is a chance that the risk to a specific subject may be much higher, or lower, than the average. This is not a problem for regulatory agencies, since they make decisions concerning the population as a whole. It *is* a problem for an IRB faced with decisions concerning particular subjects.

Uncertainty Analysis

My intent has been to show the relation between experience and rational inference, to demonstrate, both abstractly and with concrete examples, that physical experiences coupled with rational scientific reasoning does not yield a single, unequivocal "truth." Rather, the truth at any given moment is a wide array of inferences derived from applying competing models to an often ambiguous body of direct experience. Rational decisions include recognition that any one inference within this range might in fact be the "truth."

The scientific community will continue to assess this assemblage of "truths" and assign some measure of credibility to each one. Individual scientists, or the community as a whole, can then be called upon to determine a single truth on which to act. However, the extent to which inferences far from the average will be utilized in a decision, and whether a decision will be made at all, depend upon the consequences of that decision. In choosing, the scientist is looking at a different set of consequences than is a subject of human research. If the consequences are not great, it is expected that the "most likely" inference may be employed by both scientist and subject. As the risks become graver, however, these "less likely" inferences will take on added weight and meaning. In that case, one might want to act on the basis of estimates that are felt to be along the uppermost bounds of the true risk. This is probably the case today in using linear dose-response curves, although we cannot be sure. The ultimate meaning assigned to scientific estimates of risk should perhaps be the result of an integration between the estimates of potential risk and the values of the subject or patient. The most difficult task of anyone faced with making such a decision—e.g., for an IRB—is to develop a language and social system for bringing about this integration. The real meaning of any scientific estimate of risk will then emerge more clearly.

Combining all the considerations I have discussed is the intent of "uncertainty analysis." This field is currently playing a role in determining the extent to which differing estimates of radiation risk should be included in government decisions on nuclear power, waste disposal, etc. Perhaps it is time for IRB members to employ similar techniques. These techniques require that we ask questions beyond those associated with obtaining the "best" estimate of risk. In particular, one must determine whether direct experience is available and if it is similar to the proposed study. If the experience is identical with the proposed study, we must then determine if a single value has always been obtained in the past or whether different subjects show different values, such as in lung deposition. If there is some way of accounting for these differences in the past, we must ask if knowledge about the present subject can serve to determine his or her specific deposition. If such knowledge is not available, we should not profess to "know" the true deposition.

In addition, we must know whether the scientific expert has employed a specific body of experience in estimating risk (such as the atomic bomb survivors) and whether the use of other bodies of experience (such as children irradiated for diseases) might yield different estimates. We need to determine the relative strengths and weaknesses of these alternative experiences in light of the task at hand.

When models must be employed, it is necessary to determine how many such models exist within the scientific community and the extent to which each can be supported. The risk estimates arising from all such models should then be compared to determine their effect on decisions. If the models themselves require a knowledge of the physical condition of the subject, we must determine how well this condition can be specified. We must ask whether the expert is using conditions specific to the subject or whether average conditions are being assumed. If the latter is true, we need to know the extent to which these conditions might be different in the present subject.

Uncertainty analysis is not easy to perform. The person doing the analysis must understand the relation between available experience, models, and inferences. As I mentioned earlier, there may be times when the spread of possi-

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ble inferences is so small that one feels comfortable acting on the basis of the "most likely" estimate of risk. It is not possible to learn if this is true, however, until the proper questions are asked.

I have tried to point out a few key areas in which scientists may be expected to disagree, despite firm rules of reasoning. These areas will continue to exist, and members of an IRB must confront them. Technical experts have the tools to provide the necessary information for an analysis of uncertainties, even if they are not always aware of it. In the future, the role of the IRB may begin to shift from that of a passive receptacle for scientific "truths" to one that actively assumes responsibility for assigning meaning to competing estimates of scientific risk.

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