

## Slide 1

### *Causality Assessment: A Role for Biomonitoring?*

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Focus on causality assessment – a philosophical and statistical issue. It is an important topic because it explores the potential link between exposure and disease. If there is a link, is it statistical only or a deterministic causal link? What's the direction of the link?

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Can biomonitoring data provide a basis for hypothesis generation regarding cause of disease? Can it provide a basis for associating disease with exposure? Can it satisfy requirements for scientific assessment of causality; under what conditions and what types of data are needed?

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Objectives – to proceed through thought process to consider – what is the nature of a cause, what are the means of assessing a cause, what are the consequences of difference concepts, what is the nature of scientific evaluations? Will leave the conclusions to the audience.

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Henle-Koch postulates – linear and deterministic postulates that rely on mechanistic concepts of disease. Includes an experimental requirement that requires producing the disease in un-diseased animals.

Hill's Aspects of Association – Hill did not label these "Criteria" – in contrast to deterministic postulates, they are much more probabilistic. Also requires experiment – usually lost in much of the discussion (meant natural experiment – removal of exposure to see if incidence of disease decreases). Hill addressed situations in which cause cannot be established; asked, what information do we need to justify protective action.

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Linear causalism – 1 to 1 relationship - cause produces the effect. The effect is only caused by one thing. Sufficiency, necessity, specificity, unidirectionality, dose response, and externality.

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In real world, strictly linear causalism rarely occurs. Disease can be multifactorial – effect can be caused by a number of agents.

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Modifying factors can change the magnitude of effect. There can be modifying factors that increase or diminish the effects for any number of causal factors. Modifiers may or may not have an effect of their own in absence of primary causal factors. . . becomes more complex than strict linear causalism, as implied by Henle-Koch postulates, which cannot apply even to many infectious diseases.

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Complexity results in causal constellations or mosaics, where the effect is seen as the manifestation of a number of causal factors. –Not defined in a linear way, but as a portion of the cause. Factors with a low incidence overall can appear to have a disproportionate effect only because they are seen rarely. Some view causal constellation (mosaic) theory as a relaxation of causal criteria. Linear causalism can be refuted by falsifying links in the chain – Popperian approach. Other end of spectrum – refutation of a constellation / mosaic / web of events would require disproving the relevance of any factor/event, and so it becomes nearly impossible to reject any causal proposition.

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Evans analogy to criminal law – proof of guilt/cause must be established beyond a reasonable doubt or role of chance.  $P < 0.05$ ? Criteria do not define cause per se, but provide guidelines for assessing cause. Scientist often use them as an operational definition of causation. This substitution for a causation assessment can lead to errors.

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What is a cause then? That which produces an effect, that which brings about an effect, that which makes a difference? Is a difference defined scientifically, with statistical bounds on the error? Hume's definition has had far-reaching effects in philosophy and statistics - an object followed by another where if the first object had not been, the second would not have existed. Innovation is that it pivoted on clause that if C had not occurred, D would not have either – leads to concept of the counterfactual – counter to what actually occurred.

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Types of causal propositions – Johnny has cavities and loves sugar. 1) if Johnny didn't eat so much sugar, he wouldn't have cavities, therefore, sugar caused Johnny's cavities = Retrodictive causal proposition. 2) Tell Johnny that sugar *can* cause cavities, maybe you shouldn't eat it = Potential causal propositions - lacks specificity. 3) If you eat lots of sugar, you *will* get cavities = Predictive proposition. Each potential causal proposition requires counterfactual – that there is something other than what we observed to compare to. It can't be observed epidemiologically. It is not the world we see, but an inferred or constructed world.

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Is it possible that there are several possible counterfactual alternatives – ie if Johnny brushed his teeth, he may not get cavities . . . may have nothing to do with sugar. Choice of counterfactual / alternative word is determined by technical knowledge of the day, the options available for change, and our interests. Example – DNA sequencing of promotional elements that bind to transcription factors in causing lung cancer – wouldn't have been a viable counterfactual for Hill 50 years ago because he didn't know about them. Choice of counterfactual also based on options available: today we know about promoters, transcription factors and oncogenes, but we can't change a person's promoter sequences . . .but 50 years from now we may be able to change out those

promoter sequences. Knowledge of the day would affect what you can determine to be the counterfactual.

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Can alternative worlds of cause be unified if we insist on the fundamental tenets of science? 1) Identity of measurements are demonstrable and have estimates of error, 2) investigator can eliminate extraneous factors that can affect measurements . . .i.e., controlled experiment, 3) results are repeatable in independent hands. Can reliability of Hill's aspects of association be improved if each are fulfilled with data that comport to these tenets?

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Have to allow for the fact that the decisions we reach by causal analysis can be different in different situations – clinical vs. public health vs. legal. In clinic have option to remove a toxic drug, or not to, to treat with a lower dose, nutritional change, other drug (each with its own risk), but rarely have the option to do nothing, even when information is lacking. In public health and legal areas, should we have the option to determine whether there is enough scientific information to make a reasoned decision on the basis of data and knowledge about cause? If so, precaution includes the option of doing nothing because a change could be worse.

#### Slide 20

Can biomonitoring data provide a scientific assessment of cause? Do biomonitoring programs always unequivocally identify the specific disease (measurement validity)? Is the measurement of a level of chemical an accurate reflection of exposure and dose (measurement validity)? Can it be demonstrated that the individuals with the larger dose are those with the disease (error estimation)? Have all other factors been eliminated (controlled experiment)? Are the results repeatable in other populations?

#### Slide 21

What is the role for biomonitoring? Hypothesis generation? Association? Does it satisfy requirements of scientific analysis? What types of data are needed?