Toxicology 371 (2016) 12–16

Contents lists available at ScienceDirect

Toxicology

journal homepage: www.elsevier.com/locate/toxicol

Upholding science in health, safety and environmental risk assessments and regulations

Michael Aschner[a], Herman N. Autrup[b], Sir Colin L. Berry[c], Alan R. Boobis[d], Samuel M. Cohen[e], Edmond E. Creppy[f], Wolfgang Dekant[g], John Doull[h], Corrado L. Galli[i], Jay I. Goodman[j], Gio B. Gori[k,*], Helmut A. Greim[l], Philippe Joudrier[m], Norbert E. Kaminski[n], Curtis D. Klaassen[o], James E. Klaunig[p], Marcello Lotti[q], Hans W.J. Marquardt[r], Olavi Pelkonen[s], I. Glenn Sipes[t], Kendall B. Wallace[u], Hiroshi Yamazaki[v]

[a] Professor, Molecular Pharmacology, Albert Einstein College of Medicine, 1300 Morris Park Avenue, Bronx, NY 10461, United States
[b] Emeritus Professor, Institute of Public Health, University of Aarhus, Aarhus, Denmark
[c] Professor Emeritus of Pathology, Queen Mary, London, UK
[d] Professor of Biochemical Pharmacology,Department of Medicine, Imperial College, London, UK
[e] Professor, Department of Pathology and Microbiology, University of Nebraska Medical Center, Omaha, NE, USA
[f] Head of Toxicology Department, Faculty of Pharmaceutical Sciences, Université Bordeaux Segalen, Bordeaux, France
[g] Professor of Toxicology, Department of Toxicology, University of Wuerzburg, Wuerzburg, Germany
[h] Emeritus Professor, Pharmacology, Toxicology and Therapeutics, University of Kansas Medical Center, Kansas City, KS, USA
[i] Professor, Toxicology and Risk Assessment, Pharmacological and Biomolecular Sciences, University of Milan, Milan, Italy
[j] Professor of Pharmacology and Toxicology, Michigan State University, East Lansing, USA
[k] Emeritus, The Health Policy Center, Editor, Regulatory Toxicology and Pharmacology, Bethesda, MD, USA
[l] Emeritus Professor, Technical University of Munich, Munich, Germany
[m] Emeritus Director of Research INRA, Montpellier, France
[n] Professor, Pharmacology & Toxicology, Director, Institute for Integrative Toxicology, Michigan State University, East Lansing, MI, USA
[o] Affiliate Professor, Dept. of Environmental and Occupational Health, University of Washington, Seattle, WA, USA
[p] Professor, Department of Environmental Health, University of Indiana, Ellettsville, IN, USA
[q] Professor, Department of Cardiology, Thoracic and Vascular Sciences, School of Medicine, University of Padua, Padua, Italy
[r] Professor Emeritus, Experimental and Clinical Toxicology, University of Hamburg Medical School, Hambug, Germany
[s] Professor and Chair Emeritus, Department of Pharmacology and Toxicology, Faculty of Medicine, University of Oulu, Oulu, Finland
[t] Professor Emeritus, University of Arizona, Tucson, AZ, USA
[u] Professor & Associate Dean for Faculty Affairs, University of Minnesota Medical School Duluth, Duluth, MN, USA
[v] Dean of Graduate School & Professor, Drug Metabolism and Pharmacokinetics, Showa Pharmaceutical University, Machida, Tokyo, Japan

ARTICLE INFO

Article history:
Available online 14 September 2016

Keywords:
Scientific evidence
Regulation
Regulatory policy
Regulatory ethics
Animal bioassays
Hazard assessment
Risk assessment

ABSTRACT

A public appeal has been advanced by a large group of scientists, concerned that science has been misused in attempting to quantify and regulate unmeasurable hazards and risks.[1] The appeal recalls that science is unable to evaluate hazards that cannot be measured, and that science in such cases should not be invoked to justify risk assessments in health, safety and environmental regulations.

The appeal also notes that most national and international statutes delineating the discretion of regulators are ambiguous about what rules of evidence ought to apply. Those statutes should be revised to ensure that the evidence for regulatory action is grounded on the standards of the scientific method, whenever feasible. When independent scientific evidence is not possible, policies and regulations should be informed by publicly debated trade-offs between socially desirable uses and social perceptions of affordable precaution. This article explores the premises, implications and actions supporting the appeal and its objectives.

* Corresponding author.
E-mail addresses: Michael.Aschner@einstein.yu.edu (M. Aschner), ha@ph.au.dk (H.N. Autrup), colin@sircolinberry.co.uk (S.C.L. Berry), a.boobis@imperial.ac.uk (A.R. Boobis), scohen@unmc.edu (S.M. Cohen), edmond.creppy@u-bordeaux.fr (E.E. Creppy), dekant@toxi.uni-wuerzburg.de (W. Dekant), jdoull@kumc.edu (J. Doull), corrado.galli@unimi.it (C.L. Galli), goodman3@msu.edu (J.I. Goodman), gorigb@msn.com (G.B. Gori), helmut.greim@lrz.tum.de (H.A. Greim), philippe.joudrier@neuf.fr (P. Joudrier), kamins11@msu.edu (N.E. Kaminski), curtisklaassenphd@gmail.com (C.D. Klaassen), jklauni@indiana.edu (J.E. Klaunig), marcello.lotti@unipd.it (M. Lotti), marquardt@uke.uni-hamburg.de (H.W.J. Marquardt), olavi.pelkonen@oulu.fi (O. Pelkonen), Sipes@email.arizona.edu (I. G. Sipes), kwallace@d.umn.edu (K.B. Wallace), hyamazak@ac.shoyaku.ac.jp (H. Yamazaki).

[1] An Appeal for the Integrity of Science and Public Policy. Toxicology, September 4, 2016. doi:10.1016/j.tox.2016.08.015.

http://dx.doi.org/10.1016/j.tox.2016.09.005
0300-483X/

The scientific context

As a central premise of the appeal, the raison d'être of health and safety regulations is to control hazards and prevent risks, based on testable evidence provided by toxicology and epidemiology, or informed by sensible considerations of precaution. Hazards of interest entail interactions of atoms, molecules, radiations or other physical forces that can be observed and measured directly, or through instrumentation. Hazards may cause adverse effects in exposed populations when hazard potency and the intensity and duration of exposure combine to exceed no-effect thresholds. In turn, the risks of adverse effects are assessed by measuring the frequency of such effects against the intensity of hazard exposure in differently exposed and in non-exposed populations.

Epidemiology has the singular advantage of dealing with humans, and has been successful in identifying and preventing infectious diseases tied to single necessary causes. However, most chronic diseases of current interest – cancer, cardiovascular disorders and more – are linked to multiple and simultaneous hazards, which generally raise dominant barriers to unambiguous causal determinations for most retrospective epidemiologic studies. For the same reasons, prospective intervention studies have not been more successful despite subject matching and randomization efforts, which may mitigate the influence of a few variables of interest but not the bulk of multifactorial confounders of causal interpretations. Essentially, prevailing difficulties exist in measuring individual or group exposures reproducibly, and in measuring and controlling multiple externalities capable of confounding observations and results.[2]

With the exception of cigarette smoking, certain infections, and some occupational and medical exposures that can be reasonably measured, the contributions of multifactorial epidemiology to public health and policy have been precautionary—a conclusion especially true in the wake of numerous and massive intervention trials designed to test initial epidemiologic hypotheses, trials that have regularly disappointed.[3] The effective role of epidemiology is to continue investigations of occupational and other restricted settings where exposures and externalities are amenable to measurement, and to provide tentative causal clues that toxicology could investigate.

As an experimental science, toxicology is expected to follow the standards of the scientific method in attaining quantifiable evidence of physical hazards. Much has been written about the philosophical underpinnings of the method,[4] although the method and science itself would be meaningless without a few evident and essential operational standards. These ask for numerical measurement with explicit and suitably small error rates, for authentic representations of what is being measured, and for measurements that are relevant to the issues being considered, i.e. relevant to humans when testing for human hazards. They also ask for the control of externalities that may confound observations and conclusions, for detailed procedural descriptions, and for results that are reproducible by independent investigators. Ground controls should also be included to allow counterfactual inferences. Precise, authentic, relevant and reproducible measurements are the foundations of reliable scientific evidence.[5]

Unlike the absolute truths of purely intellectual disciplines, such as mathematics, geometry and formal logic, natural sciences postulate empirical truths in a probabilistic context, because of the inherent approximations of measurements, the multitude of potentially confounding variables and the natural vagaries of atoms, molecules and overall matter. Although philosophically provisional, such truths – or natural laws – are generally verified counterfactually by reliable controls and applications: airplanes fly, radio waves convey signals, and therapies cure. Indeed, it is the operational standards of the scientific method as just described, which have allowed science to accumulate a body of empirical knowledge sufficiently certain to enable all successful technologies and applications that sustain advanced societies.

Empirical science also includes a research activity dealing with knowledge-in-the-making, aiming at validating emerging hypotheses to virtual certainty. Yet, hypotheses are not theorems, and research conjectures and preliminary findings are scientific in the sense of being part of scientific research, but are not part of the validated and operational knowledge of science.[6] Thus, as the appeal implies, it should be unethical to use untested research presumptions in justifying policies and regulations that substantially interfere with national economies, that influence the anxieties, choices and behavior of billions of citizens, and that can impose massive penalties and even detention on transgressors. In this light, the appeal maintains that hazards characterized by the scientific method can justify regulation on their own account—a justification that is not permissible when the significance of putative hazards cannot be assessed empirically.

Testing for and measuring human hazards

For ethical and practical reasons, tests for the regulation of potential human hazards are conducted in animals, mostly rats and mice. Although animals are not Man, short-term animal tests offer experimentally verifiable insights on short-term adverse effects in animals and humans, and on the threshold exposure conditions

[2] Green, M.D., Friedman, D.M., Gordis, L. *Reference Guide on Epidemiology*. Reference Manual on Scientific Evidence, Third Edition. Federal Judicial Center, National Research Council. National Academy Press, Washington DC. 2011. http://www.fjc.gov/public/pdf.nsf/lookup/SciMan3D12.pdf/$file/SciMan3D12.pdf

[3] Werkö, L. *The enigma of coronary heart disease and its prevention*. Acta Med Scand. 1987;221:323–333. Werkö, L. *Analysis of the MRFIT screens: A methodological study*. J. Int. Med. 1995;237:507–518. Hakama M., Beral V., Cullen J., Parkin M. *UICC workshop on evaluating interventions to reduce cancer risk*. Int. J. Cancer. 1989;43:967–969. Strandberg T.E., Salomaa V.V., Vanhanen H.T., Neukkarinen V. A.; Sarna S.J., Miettinen T.A. *Mortality in participants and non-participantsof a multifactorial prevention study of cardiovascular diseases: A 28 year follow up of the Helsinki Businessman Study*. Br. Heart J. 1995;74:449–454. Luepker R.V., Murray D.M., Jacobs D.R., Mittelmark, M.B., Bracht N., Carlaw R., et al.; *Community education for cardiovascular disease prevention: risk factor changes in the Minnesota Health Program*. Am. J. Publ. Health. 1994;84:1383–1393. The Multiple Risk Factor Intervention Trial Research Group. *Mortality after 16 years for participants randomized to the Multiple Risk factor Intervention Trial*. Circulation. 1996;94:946–951. Feinlieb M.; *New directions for community intervention studies*. Am. J. Publ. Health. 1997;86:1696–1698. Shaten J.B., Kuller L.H., Kjeselberg M.O., Stamler J., Ockene J.K., Cutler J.A., et al.; *Lung Cancer Mortality after 16 years in MRFIT Participants in Intervention and Usual-Care Groups*. Ann. Epidemiol. 1997;7:125–136. Taubes G.; *The soft science of dietary fat*. Science. 2001;291:2536–2545. Taubes G.; *Epidemiology faces its limits*. Science 1995;269:164–169. Editorial; *Do epidemiologists cause epidemics?* Lancet 1993;341:993–994.

[4] Gauch H.G., Jr.; *Scientific Method in Practice*. Cambridge University Press, Cambridge, UK, 2003.

[5] Hand D.J.; *Measurement theory and practice. The world through quantification*. Arnold, London, UK, 2004.

[6] Berry, Sir Colin; *Relativism, Regulation and the Dangers of Indifferent Science*. Toxicology 2010; 267; 7–13. Gori G.B.; *Science, Imaginable Risks, and Public Policy: Anatomy of a Mirage*. Regulatory Toxicology and Pharmacology. 1996;23:304–311.