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Good Laboratory Practices: Myers et al. Respond

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We are in complete agreement with the statement by Becker et al. that "having confidence in scientific procedures and data is the *sine qua non* for determining the safety of chemicals and chemical products." Our aim in writing the commentary (Myers et al. 2009) was not to challenge the original intent of Good Laboratory Practices (GLP) requirements, which was to establish standards of record keeping in contract laboratory research so as to reduce the likelihood of fraud. Our goal instead was to show—through an analysis of the application of GLP data on bisphenol A (BPA) in regulatory proceedings—that GLP by itself is insufficient to guarantee valid and reliable science. Becker et al. appear to have missed the point of our commentary entirely.

In the case of BPA, three GLP studies have been offered by industry-sponsored laboratories as proof of the chemical's safety (Cagen et al. 1999; Tyl et al. 2002, 2008). Each has errors in study design and/or data interpretation that are sufficiently serious as to invalidate the conclusions of these studies (Myers et al. 2009). Nevertheless, because the studies were conducted using GLP guidelines, they were judged by regulators as being more reliable than the many National Institutes of Health (NIH)-funded and peer-reviewed studies that have reported adverse effects (Richter et al. 2007; vom Saal et al. 2007).

As our commentary (Myers et al. 2009) clearly establishes, GLP did not guarantee the scientific validity of these three studies. Because previous analyses had identified serious flaws in the first two of those GLP studies, we focused critical attention on the most recent (Tyl et al. 2008), which both the European Food Safety Authority (EFSA 2006) and the U.S. Food and Drug Administration (FDA) had identified as key in their BPA risk assessments (FDA 2008). We found three main flaws: *a*) the animals were inexplicably insensitive to estrogen; *b*) the assays were outdated and insensitive compared with methods used in NIH-funded research showing adverse effects; and *c*) validity of the findings was challenged. For example, the prostate weights of control animals reported by Tyl et al. (2008) were > 70% larger (mean, > 72 mg) than those reported by numerous laboratories, including a previously published study using CD-1 mice [conducted at RTI, where the study by Tyl et al. (2008) was conducted] that reported mean prostate weights of 46 mg in CD-1 males that were examined at a similar age (Heindel et al. 1995).

Since we published our commentary (Myers et al. 2009), a possible contributor to both the estrogen insensitivity and the enlarged control prostates has been suggested: Approximately 3 years before the experiments that formed the basis of the study by Tyl et al. (2008), there was a polycarbonate fire that released BPA into the RTI laboratory where the research was conducted (Kissinger and Rust 2009). An investigation revealed that animals in the laboratory were exposed to low doses of BPA that government-funded science (Richter et al. 2007) indicates could affect research animals.

Additional uncertainties about Tyl et al.'s study (Tyl et al. 2008) have now been identified by the lead author. Whereas the published paper reports that the animals were examined at approximately 14 weeks of age, Tyl testified at an FDA hearing in September 2008 that they were 6 months of age, and then at a German Environmental Protection Agency hearing in March 2009 that they were 5 months of age (Kissinger and Rust 2009). There she confirmed that the information in the original article was inaccurate. Because an animal's physiology changes as it ages, these contradictory statements are problematic for all reported outcomes; even at 5–6 months of age, normal, healthy CD-1 male mice would not have the grossly enlarged prostates reported by Tyl et al. (2008).

The use of flawed science, however, is not the only concern. The type of multigeneration testing approach used in these studies is, quite simply, insufficient for the testing of endocrine-disrupting chemicals. This is not a new concept. The need for more specific tests for endocrine-active compounds led in 1998 to the establishment at the U.S. Environmental Protection Agency (U.S. EPA) of the Endocrine Disruptor Screening Program, mandated by Congress (U.S. EPA 1998). After virtually no progress for over a decade, in 2009 the U.S. EPA finally announced a set of testing procedures that will be examined. The proposed "new" methodology, heavily dependent upon traditional toxicologic methods used in multigenerational GLP studies, is still woefully inadequate (Colborn 2009).

The letter by Becker et al. provides a striking example of the reluctance of industry lobbyists to hear this message. In the eyes of the 36 scientific colleagues who coauthored our commentary (Myers et al. 2009), the BPA studies that Becker et al. attempt to defend are so seriously flawed as to be indefensible. Rather than continue to defend a dead issue, we encourage industry representatives to come into the 21st century and help us devise new paradigms for testing endocrine-disrupting chemicals that will safeguard human health.

The authors' freedom to design, conduct, interpret, and publish this letter was not nor is compromised by any controlling sponsor as a condition of review and publication.

J.P. Myers is CEO/chief scientist for Environmental Health Sciences (EHS), a not-for-profit organization that receives support from several private foundations (listed at http://www.environmentalhealthnews.org/about.html) to support EHS's mission to advance public understanding of environmental health sciences; no grants to EHS were received to support the writing of this letter. T. Colborn is the president of TEDX (The Endocrine Disruption Exchange), a not-for-profit organization receiving funding from several private foundations (listed at http://www.endocrinedisruption.com/support.php) in support of their mission to educate people about endocrine disruption and other toxic chemicals, and to assist them in their efforts to reduce the production, use, and exposure to chemicals that can interfere with development and function; TEDX also receives individual contributions solicited via the website. S. Jobling is the principal of Beyond the Basics

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Electromagnetic Fields and the Precautionary Principle

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Since Galileo, debates in science are supported by logical reasoning and reference to statements of fact and not by reference to "authorities." Consequently, literature serves or should serve two purposes: to give credit to thoughts expressed earlier by others, and to refer to statements of facts.

The article by Dolan and Rowley (2009)—employees of the mobile telephone industry—is an example of a compilation of points of views expressed by authorities. No number of references to authoritative statements can replace scientific discourse. The article can be summarized as follows: There is no convincing evidence of harm from exposure to microwaves below levels recommended by the International Commission on Non-Ionizing Radiation Protection (ICNIRP) (1998); therefore, there is no harm, and hence application of the precautionary principle is not indicated.

Indeed, the precautionary principle is not intended as a response to unfounded fears of the public or to aim at zero risk, but as a risk management strategy in case of scientific uncertainty about the existence or magnitude of a risk. Apparently Dolan and Rowley (2009) are not aware that their subjective reasoning does not differ from the unfounded fears of the public and can be summarized as "unfounded reassurance of no harm."

In principle, ethical considerations, value judgments, and consensus play an important role when giving guidance to public health policy. This is because "it is impossible to derive . . . a proposal for a policy from a sentence stating a fact" (Popper 1945). Use of subjective terms such as "sufficient evidence" (let alone "convincing evidence"— convincing for whom?) or "adverse effect" is unavoidable. Referring to the World Health Organization (WHO 2000), Dolan and Rowley (2009) stated: "The corresponding advice to governments is to adopt science based guidelines and not to undermine confidence by incorporating additional arbitrary safety factors." The expression "science-based guidelines," if taken literally, is a contradiction in terms. Although public health guidelines should be based on a thorough risk assessment, neither the assessment itself nor the reasoning that is applied to derive a guideline can be scientific. No scientific evidence can define a margin of safety; no scientific evidence can replace the value judgment of which evidence to rely on, which evidence to dismiss, and so forth. Safety factors are always—at least to certain degree—arbitrary. For example, we very rarely have scientific evidence about the distribution of sensitivity to a toxic agent in the population; therefore, we apply arbitrary factors for taking interindividual differences into account. What is important, and nearly always neglected in the area of electromagnetic fields (EMF), is to clearly state where value judgments and arbitrary decisions entered the argument and the derivation of guidelines.

The international standards for EMF (ICNIRP 1998; IEEE 2006) are based on immediate effects of exposure, such as excitation of nerve or muscle cells for low-frequency fields and increase of body temperature for high-frequency fields, not because there are no other effects, even at levels far below the guideline levels derived from these acute effects, but because the panels came to the consensus that these other effects cannot (yet) form the basis for the derivation of guidelines. For example, the International Agency for Research on Cancer (IARC 2002) classified power frequency magnetic fields as a possible human carcinogen. In that case, the subjectivity of the assessment is fully transparent: The basic rules of IARC were violated, as the panel questioned whether epidemiologic evidence can be causally interpreted in spite of evidence that neither bias nor confounding accounts for the increased childhood leukemia risk. The exposure level for which there is evidence of an increased childhood leukemia risk is far below the international standards, but the panels setting the standard did not use this evidence as a basis for the derivation of a guideline level for power frequency fields. There are surely many arguments for this decision. However, none are scientific. This is not meant as a reproach, because we recognize the fact that guidelines cannot be derived from scientific statements alone.

It would be much more appropriate if Dolan and Rowley expressly stated that they are completely satisfied with the international standards and that the industry does not want to be bothered by allusions to precaution.