How to overcome limitations of new regulatory approaches methodologies in the context of regulatory science.

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For a long time, animal toxicology has been the major source of information on chemical risk assessment. New regulatory policies (e.g., REACH, Cosmetics) tend to drastically reduce the use of animals, so there is large space for opportunities to accept "alternative" approaches, both *in vitro* and theoretical (QSAR) ones. This has stimulated a new focus on the elucidation of the details of mechanisms of toxicological action (e.g., AOPs, Tox21) as a basis to build predictive models. A key question is: are the proposed alternative methods able to predict correctly the Apical toxicological endpoints of regulatory relevance? This is very important, because: a) the Apical toxicological endpoints are at the basis of present regulations; b) correct predictivity is the necessary, ultimate check of the validity of any theory or hypothesis. This paper studies alternative toxicological approaches by putting into perspective new (Skin Sensitization, Toxcast) and previous (Carcinogenicity) case studies. Quantitative modeling of rate-limiting steps in Skin sensitization and Carcinogenicity predicts the majority of toxicants. Similarly, successful QSAR models exploit the quantification of only one, or few rate-limiting steps. High-throughput assays within Toxcast point to promising associations with endocrine disruption, whereas markers for pathways intermediate events have limited correlation with most endpoints. Since the types of pathways may be very different (often not simple linear chains of events), a rigorous quantitative analysis is necessary to identify the type of mechanism, the relative quantitative weight of each event, and to build the appropriate predictive model.