## 2179 The Potential Impact of the NIOSH Chemical Carcinogen Policy on NIOSH Recommendations

C. Whittaker[1], P. A. Schulte[1], R. D. Daniels[1], K. MacMahon[1], T. J. Lentz[1], J. Piacentino[2], and J. Howard[2]. *[1]CDC/NIOSH, Cincinnati, OH; and [2]CDC/NIOSH, Washington, DC.*

NIOSH has published the *Current Intelligence Bulletin: NIOSH Chemical Carcinogen Policy* to address three issues: carcinogen classification, how NIOSH risk management limits are set and how information on the analytical limit of quantification (LOQ) is used in NIOSH recommendations. The classification policy updates current practice to allow NIOSH to adopt chemical carcinogen classifications from the National Toxicology Program, the Environmental Protection Agency and the International Agency for Research on Cancer. The risk management limit policy updates the risk level at which NIOSH recommendations are set and redefines NIOSH recommendations as risk management limits for carcinogens (RML-CA). Historically, NIOSH issued recommended exposure limits (RELs) for carcinogens based on an excess risk of level of 1 in 1,000 in a working lifetime, while still acknowledging that there is no safe level of exposure to carcinogens. Under a new policy, NIOSH may set RML-CAs at the concentration corresponding to the 95% lower confidence limit of the 1 in 10,000 risk estimate, but only when occupational measurement of the carcinogen at the RML-CA is analytically feasible. To understand the impact of these potential changes on future NIOSH recommendations, preliminary risk assessments were conducted on 20 chemicals with sufficient data for analysis but without a current numerical REL. The 95% confidence limits for the 1 in 10,000 risk level were calculated and the result was compared with a 1 in 1000 risk level and with the analytical LOQ. The LOQ for 50% of the chemicals analyzed was greater than the lower 95% confidence limit on 1 in 10,000 risk. When compared to the lower 95% confidence limit of 1 in 1000 risks for these same chemicals, the LOQ was greater than the lower 95% confidence limit only 30% of the time. Although this analysis represents a limited sample size, it shows that a subset of NIOSH RML-CAs can be set based on the analytical LOQ rather than the risk estimate. It is therefore critically important that the risks at the RML-CA are communicated to end users. *(The findings and conclusions in this presentation are those of the authors and do not necessarily represent the views of the National Institute for Occupational Safety and Health).*

## 2180 Differences in SEND Dataset Creation: Analysis of Current Situation and Points to Consider

G. Sato[2,4], Y. Sakakibara[2,7], A. Hamada[2,6], T. Uota[2,1], M. Yoshiike[2,3], and Y. Fujimura[2,5]. *[1]CAC Croit Corporation, Chuo-ku, Osaka, Japan; [2]CDISC Japan User Group (CJUG) SEND Team, Minato-ku, Tokyo, Japan; [3]Daiichi Sankyo Co., Ltd., Shinagawa-ku, Tokyo, Japan; [4]Eisai Co., Ltd., Tsukuba, Ibaraki, Japan; [5]Fujitsu Systems East Limited, Minato-ku, Tokyo, Japan; [6]Japan Tobacco Inc., Chuo-ku, Tokyo, Japan; and [7]Kyowa Hakko Kirin Co., Ltd., Sunto-gun, Shizuoka, Japan.*

When considering development of a new drug in the United States, preparation of SEND package consisting of SEND Datasets, Define.xml, and SDRG, will become a regulatory mandate for certain types of nonclinical toxicology studies starting from December 2016 for NDA/BLA submissions. Although SEND is a CDISC Standard for nonclinical studies, the actual SEND Datasets may differ among different facilities due to different SEND file creation computer systems. There is, however, very limited information available to understand details of such differences. The CJUG SEND Team investigated the current situation of "differences" in SEND Datasets creation following IG Version 3.0, by collecting examples of a number of facilities' specifications (mapping details) on an anonymous basis, categorized them, and summarized "Points to Consider" when accommodating such differences in preparing SEND package. Our preliminary analysis revealed that the differences could be categorized into several levels, including how to describe a variable (e.g. USUBJID: S12345-M001 vs. S12345_M001), whether to include a variable (i.e. many of Permissible variables), and whether to create a domain (e.g. creation of CO domain). We assumed that these differences could essentially come from different objectives of SEND Dataset creations, such as maintaining integrity through a product when merging Datasets from different facilities, data exchange among studies, products, and organizations/different companies which may lead to a creation of big database. [Abbreviations] BLA = Biologics License Application, CDISC = Clinical Data Interchange Standards Consortium, CJUG = CDISC Japan User Group, CO = Comments, IG = Implementation Guide, NDA = New Drug Application, SDRG = Study Data Reviewer's Guide, SEND = Standard for Exchange of Nonclinical Data.

## 2181 Stepwise Screening Scheme for Identification of Animal Testing Alternatives

R. A. Wess. *Envigo CRS (Switzerland) Ltd., Füllinsdorf, Switzerland.* Sponsor: L. Coney.

When seeking for registration of a substance, GLP-guideline studies are normally employed on the substance as test item to obtain the basis for an assessment as required by the applicable guidance. Nonetheless there could be other possibilities to reach a meaningful conclusion. Furthermore a systematic evaluation assures avoidance of test artefacts, which may not only produce unnecessary cost and animal consumption, but also the requirement to repeat a study. Generally the following options should therefore be considered first. 1. Waiving an endpoint - Not assessing on an endpoint information requirement A short-term effect study may be unnecessary when long-term exposure results exist. In such case the acute toxicity testing may be omitted. 2. Waiving an experiment - Not testing for an endpoint information requirement Apart from the three standard waiving arguments, i.e. • testing does not appear scientifically necessary because existing (literature) data suffice, • testing is technically not possible and • exposure based (below adequate Threshold of Toxicological Concern), assessment of one endpoint by data from a different one can be possible: • Endpoint-Analogy Read-Across: e.g. chronic fish toxicity from a carcinogenicity study using fish (US NTP protocol) 3. Analogy approaches (equimolar basis) Experimental evidence can be used from tests with surrogates or analogues: • Surrogates: Identical chemical species liberated (source chemical) withanalogue bioavailability due to degradation kinetics or dissociation ___o "Prodrug" target chemical forms source chemical as primary degradant ___o "Converging pathway"degradation pathways of source and target chemicals lead to formation of a common degradant known to produce the effect ___o "Actual exposure"different but non-toxic and thus irrelevant counterion after dissociation • Analogues: Identical bioavailability after lipophilicity based correction ofanalogue chemical species sharing a mode of action ___o One-to-one read-across from only one chemical ___o Trend analysis (QSAR) within a larger group forming a category 4. Mixture effect evaluation and calculationsIn a "prodrug" case, if a substance is cleaved into two new substances whereof one is suitable for read-across, both may contribute to the overall effect. Also known impurities should be assessed using the appropriate model (independent or combined action).

## 2182 Replacing Animals for Acute Systemic Toxicity Testing: A US Strategy and Roadmap

A. Lowit[5], C. Schlosser[5], A. Myska[1], G. Patlewicz[4], M. Paris[2], A. Karmaus[2], J. Strickland[2], D. Allen[2], N. Kleinstreuer[3], and W. Casey[3]. *[1]DOD/DTRA, Ft. Belvoir, VA; [2]ILS, Research Triangle Park, NC; [3]NIEHS, Research Triangle Park, NC; [4]US EPA, Research Triangle Park, NC; and [5]US EPA, Washington, DC.*

ICCVAM is contributing to a US strategy and roadmap for implementing 21st century toxicity testing approaches by promoting alternative approaches for acute systemic toxicity testing. Development and implementation of these approaches will involve four key steps: (1) defining testing needs, (2) identifying available alternatives, (3) developing integrated approaches to testing and assessment (IATA), and (4) addressing both scientific and non-scientific challenges. Each of these steps was considered in a 2015 workshop (http://ntp.niehs.nih.gov/go/atwksp-2015) which explored how to move alternative approaches for acute systemic toxicity testing from research to regulatory testing. Our review of US and international testing needs highlighted that, while there are regional differences in specific testing requirements, all currently accepted guidelines for these tests share core principles. These include essential testing needs to be addressed by alternative approaches and opportunities for existing information to enable waivers of required testing. For example, guidance recently published by US EPA on waiving the acute dermal toxicity test was based on a NICEATM analysis that demonstrated how sufficient hazard labeling was obtained with acute oral toxicity test information alone. While a variety of available alternative test methods can reliably identify potential cytotoxicants, none can single-handedly assess the multiple mechanisms of acute systemic toxicity following oral, dermal, or inhalation exposure. Accordingly, IATA will need to be developed to address the breath of different mechanisms, ensure good coverage of the chemical landscape of interest and leverage the collective strengths of the most promising test and non-test methods. Finally, to ensure that the scientific and non-scientific considerations that could impede the adoption and implementation of such approaches are addressed, input will be needed from industrial sectors, academic disciplines, federal agencies, stakeholder organizations, and international partners. *(This project was funded in whole or in part with Federal funds from the NIEHS, NIH under Contract No. HHSN273201500010C. This abstract does not necessarily represent US EPA policy).*


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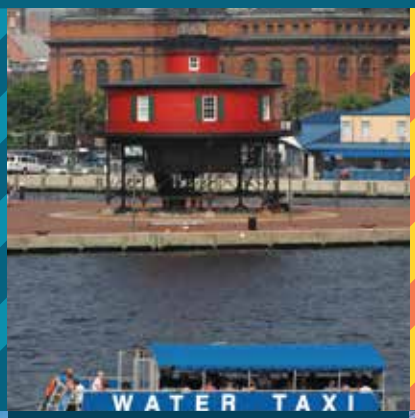


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