studies/endpoints led by academic investigators. Twelve extramural grantees were selected by NIEHS through an RFA-based initiative to participate in the overall study design and conduct disease-relevant investigations using tissues and animals from the core study. While the study is expected to contribute to our understanding of potential effects of BPA, it also has ramifications beyond this specific focus.Through CLARITY-BPA, NIEHS has established an unprecedented level of collaboration among extramural grantees and regulatory researchers. The CLARITY-BPA represents a potential new model for filling knowledge gaps, informing chemical risk assessment, and identifying new methods or endpoints for regulatory hazard assessments.

PS 1571 How Consistent Are the Derived No-Effect Levels (DNELs) in the European REACH Legislation?

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The new European REACH regulation places more responsibility than hitherto on manufacturers and importers of chemicals ("industry") to provide safety information. An important part of the development of a REACH Chemical Safety Report is derivation of Derived No-Effect Levels (DNELs) which represent "the level of exposure above which humans should not be exposed". In order to study the consistency, we compared DNELs presented by industry at the website of the European Chemicals Agency (ECHA) with those derived by us in our interpretation of the REACH guidance (Chapter R.8: Characterisation of dose [concentration]-response for human health, http://echa.europa.eu/documents/10162/13632/information_requirements_r8_en.pdf). There are various DNELs, e.g. representing short-term, long-term, inhalation and dermal exposure, as well as workers and the whole population. We limited our study to "worker-DNELs long-term" for inhalation route as they resemble occupational exposure limits (OELs). We found 24 substances for which (1) such DNELs were given in the ECHA chemical database (http://echa.europa.eu/web/guest/information-on-chemicals/registered-substances) and (2) a scientific basis for OEL had been published by the Swedish Criteria Group within the last 15 years in the serial Arbete och Hälsa (https://gupea.ub.gu.se/handle/2077/3194?locale=en). The results were startling, as the DNELs given by industry were 2.4 to 1,100 times higher than ours for 23 substances and 260,000 times higher for trimellitic anhydride. Some of the discrepancy is explained by different choice of key studies/points of departure (PODs). However, the choice of assessment factors (AFs) also differed markedly, as industry's total AFs (calculated implicitly from the POD and the DNEL) were 1-230 times lower than ours. We conclude that although the REACH guidance is relatively detailed, many arbitrary choices remain that will influence the DNEL. A major problem is that little advice is given on when and how to depart from default AFs.

PS 1572 Animal Use for Testing Involving Unrelieved Pain and Distress.

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Each facility in the United States that uses live animals for research, tests, experiments, or teaching must submit an annual report to the U.S. Department of Agriculture (USDA) that includes "the common names and the numbers of animals upon which experiments, teaching, research, surgery, or tests were conducted involving accompanying pain or distress to the animals and for which appropriate anesthetic, analgesic, or tranquilizing drugs were (or were not) used" (9 CFR, Chapter 1 Part 2, Section 2.36). In accordance with the definitions in §2132 of the Animal Welfare Act (7 U.S.C. 54), it is not necessary to report birds, rats of the genus Rattus and mice of the genus Mus bred for use in research, or fish, amphibians and livestock or poultry used in agricultural research. In the 2010 USDA annual report on animal usage, a total of 1,134,693 animals were reported, with 97,123 of those reported as experiencing unrelieved pain and distress. Based on an analysis of these data by the National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM), 95% (91,997/97,123) of the animals reported to the USDA as experiencing unrelieved pain and distress were used for testing. Of these animals, 57% (54,889/97,123) were used for vaccine testing, and 38% (37,108/97,123) were used for toxicity testing. Most of the animals used for toxicity testing were used for safety testing and drug efficacy testing. NICEATM is currently investigating and promoting alternative test methods to further reduce the number of animals used in painful procedures. Supported by ILS staff under NIEHS Contract N01-ES-35504.

PS 1573 A Reference Database for the Evaluation of Alternative Tests for Acute Dermal Systemic Toxicity.

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Alternatives for acute systemic toxicity testing are one of the highest priorities of ICCVAM and NICEATM. These are the most commonly performed product safety tests worldwide and are required by multiple U.S. Federal agencies. Acute toxicity testing can involve large numbers of animals and result in significant unrelieved pain and distress to test animals. High quality reference data are needed to evaluate alternative toxicity tests that may reduce, refine (enhance animal well-being and lessen or avoid pain and distress), and replace the use of animals for acute dermal systemic toxicity testing. To identify appropriate reference data for the acute dermal systemic toxicity test, NICEATM collected and analyzed data for 1897 substances. Rabbits were used for 28% (526) of the studies, and rats were used for 72% (1371). Of the 1897 substances, 84% (1598/1897) had data for both male and female animals, and 98% (1561/1598) of those substances were in the same GHS dermal hazard category. For the 37 substances that showed a different dermal hazard category between the sexes, female values were more often in a higher hazard category (21 for females vs. 16 for males). Two hundred forty six studies reported day of death. Approximately two thirds of the deaths (67% of male deaths [513/761]; 63% of female deaths [463/733]) occurred by Day 2 after a 24-hour dermal treatment on Day 0. Eighty-five substances had sufficient data to calculate dermal dose–mortality slopes. Dose–mortality slopes did not vary by species, sex, or GHS hazard category. As expected, the dermal dose–mortality slopes were lower than acute oral dose–mortality slopes. These data were used to design a proposed sequential test for acute dermal systemic toxicity, the dermal up-and-down procedure, to reduce the number of animals tested for acute dermal hazard classification. Supported by ILS staff under NIEHS Contract N01-ES-35504.

PS 1574 Regulatory Acceptance of the BG1Luc Estrogen Receptor Transactivation Test Method.

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NICEATM coordinated an international interlaboratory validation study of the BG1Luc estrogen receptor transactivation test method (BG1Luc ER TA, LumiCell®) developed by Xenobiotic Detection Systems, Inc. In 2010, the validation study completed its goal to evaluate the usefulness and limitations of the BG1Luc ER TA test method to screen for substances with in vitro ER agonist or antagonist activity. The international validation study was sponsored by NICEATM, with participation from the European Centre for the Validation of Alternative Methods, and the Japanese Center for the Validation of Alternative Methods. In 2012, NICEATM–ICCVAM released a test method evaluation report on the usefulness and limitations of the BG1Luc ER TA test method. ICCVAM recommended the use of the BG1Luc ER TA as a screening test to identify substances with in vitro ER agonist and antagonist activity and recommended that the BG1Luc ER TA test method could be considered as an alternative to the existing ER TA test guideline (EPA OCSPP 890.1300/OECD TG 455). All 15 ICCVAM member agencies, including the US Environmental Protection Agency, concurred with the ICCVAM recommendations. NICEATM sponsored the new method for evaluation by the Organisation for Economic Co-operation and Development (OECD), which approved the BG1Luc test method and added the BG1 agonist protocol to the existing Test Guideline 455. The BG1 antagonist method has been adopted as OECD Test Guideline 457. Acceptance of the BG1Luc ER TA test method by U.S. and international agencies is an example of increased cooperation and collaboration to support the international adoption of scientifically valid test methods that will protect people, animals, and the environment while reducing, refining, and replacing animal use. Supported by ILS staff under NIEHS Contract N01-ES-35504.

PS 1575 Quantitative Risk Assessment As the Basis for a Proposed NIOSH Recommended Exposure Limit for Hexavalent Chromium Compounds.

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Sponsor: D. Dankovic.

To update the National Institute for Occupational Safety and Health (NIOSH) recommendations for protecting workers with occupational exposure to Cr(VI) compounds, all aspects of occupational exposure to and control of hexavalent

chromium compounds (Cr(VI); e.g., chromic acid, CAS No. 1333-82-0; sodium dichromate, CAS No. 7789-12-0) were evaluated including epidemiology, toxicology, risk assessment, analytical methods, and industrial hygiene practices. Derivation of a proposed Recommended Exposure Limit (REL) was one component of the updated risk management recommendations. The NIOSH proposed REL was derived based on the results of a quantitative risk assessment (QRA) of lung cancer in chromate production workers. The NIOSH REL was previously based on the quantitative limitation of the 1975 analytical method; at that time NIOSH recommended that occupational carcinogens be controlled to the lowest feasible concentration. Data from a cohort of Baltimore chromate production workers were selected for analysis due to the availability of extensive exposure assessment data, information about smoking histories, strong statistical power, and relative lack of confounding exposures. Excess lifetime risk at the REL of 1 μg Cr(VI)/m3 was estimated as 6 (95% confidence limits=3-12) lung cancer deaths per 1000 workers. Based on these results, NIOSH proposed a REL of 0.2 μg Cr(VI)/m3 8-hour time-weighted average exposure during a 40-hour workweek. The proposed REL has an estimated working lifetime (45 years) excess risk of lung cancer mortality of approximately one in 1000. NIOSH, Occupational Safety and Health Administration, and international consensus standard analytical methods can accurately quantify workplace exposures at the proposed REL. Recommending the control of occupational Cr(VI) exposures to below the proposed REL is intended to reduce the incidence of work-related lung cancer.

PS 1576 The Dermal Up-And-Down Procedure: An Alternative Test Method for Acute Dermal Systemic Toxicity Testing.

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Acute dermal systemic toxicity testing is required to identify chemicals and products that have the potential to cause life-threatening or fatal toxicity following skin exposures. Such testing is one of the five most commonly conducted safety tests and requires up to 20 or more animals per test. A dermal up-and-down procedure (UDP) was developed to estimate acute dermal toxicity hazard classification categories with fewer animals. The UDP incorporates an efficient experimental design using sequential testing to estimate LD50 rather than the simultaneous testing of multiple groups of animals at multiple doses, as specified by current regulatory test guidelines. In the dermal UDP, individual animals are dosed sequentially, and the response of each animal after 48 hours is used to determine the dose applied to the next animal. If a dose produces significant toxicity, the next animal is tested at a lower dose. Conversely, if no significant toxicity is observed, the next animal is tested at a higher dose, with the highest dose not to exceed a pre-specified limit dose. Unless there is a basis for a lower starting dose, the initial dermal UDP starting dose is the appropriate limit test dose (2000 or 5000 mg/kg). The default dose-progression factor for subsequent doses is 4.2. If the expected LD50 is less than the default starting dose, testing is started at one dose below the closest default dose. Using a starting dose of 5000 mg/kg, default doses are 5000, 1200, 300, 70, 15, and 4 mg/kg, while the default doses for a starting dose of 2000 mg/kg are 2000, 500, 100, 25, and 5 mg/kg. The dermal UDP provides LD50 point estimates and confidence limits for dermal hazard classifications while using up to 85% fewer animals. The proposed dermal UDP can support accurate hazard identification while significantly reducing animal use. Supported by ILS staff under NIEHS Contract N01-ES-35504 and SRA staff supported by NIEHS Contract GS-23F-9806H.

PS 1577 Fatal Misuse of Humidifier Disinfectants in Korea: Importance of Screening Risk Assessment and Implications for Management of Chemicals in Consumer Products.

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The Korea Centers for Disease Control and Prevention (KCDC) reported on August 31, 2011 that the unidentified fatal lung disease found in Korea might have been caused by chemical disinfectants used with household humidifiers. Among them, four patients passed away because of the rapid development of pulmonary fibrosis after long exposure to the disinfectants over several months. A provisional conclusion by an epidemiological investigation that active ingredients of disinfecting products (polyhexamethyleneguanidine (PHMG) and oligo(2-(2-ethoxy)ethoxyethyl guanidinium chloride (PGH)) caused this disease was reinforced by a subsequent inhalation toxicological study using rats. In Korea, humidifier disinfectants have been put in the water tanks of humidifiers for the prevention of germs, mold, and/or algae. The disinfectants were manufactured and sold on the market without any data on inhalation toxicity being submitted and without risk evaluation on an industrial or government level. We conducted a screening-level risk assessment for the disinfectants. With these high values of the risk quotients for PHMG and PGH containing the guanidine moiety, it should have been possible to screen the chemicals with potential health concerns before their introduction to the market. Precautionary measures such as "premarket registration and evaluation" and "significant new use notice and re-evaluation" need to be complemented by post-market control systems such as product recall and health surveillance systems to screen the health hazards of chemicals.

PS 1578 Multiple Federal Hazard Assessment Programs—A Relevant Information or Redundant Efforts?

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Much interest, at both the Executive and Legislative levels, is currently directed towards evaluating how to reform and streamline government to improve efficiencies and decrease costs. In Jan. 2010, President Obama, acknowledging challenging economic times, began an effort to decrease waste and inefficiencies in the government. Similarly, Public Law 111-139 (2010) required the Government Accountability Office to identify federal programs with duplicative goals and activities. Regarding the evaluation of hazards associated with environmental contaminants, there are at least three Federal programs that have seemingly overlapping, although not perfectly aligned goals. Our question was: Do these government programs provide novel information or are the efforts redundant? While the EPA Integrated Risk Information System (IRIS) evaluates risk information for chronic non-cancer and cancer effects, the Agency for Toxic Substances and Disease Registry (ATSDR), in its Toxicological Profiles, evaluates non-cancer effects at acute, sub-chronic and chronic exposures. The National Toxicology Program's Report on Carcinogens (RoC) provides cancer descriptors, as does the IRIS Program, although NTP does not develop quantitative risk values. The IRIS Reference Values and the ATSDR Chronic Minimal Risk Levels were examined. Additionally, the IRIS and NTP cancer classifications for substances were also reviewed. If the same substance was evaluated by two programs, we also compared the final Agency recommendations. Significant findings will be presented. For example, the analyses show that even though the IRIS program has evaluated over 550 chemicals there are only 85 chemicals with Reference Concentrations (RfC) and since 1995 EPA releases, on average, 3 new RfCs a year. Similarly, although ATSDR has evaluated over 170 chemicals, there are only 42 with chronic inhalation values and approximately half of these chemicals are the same ones EPA evaluated. The full analysis of results will help the agencies and stakeholders assess the value in supporting three separate programs.

PS 1579 Utilization of Benzene Chromosomal Biomarkers by US Courts in Adjudicating Causation.

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This study evaluates the utilization of chromosomal biomarkers in court cases that involved benzene exposure, one of the first major set of cases to rely on biomarker data. The methodology involved searching the Westlaw database for all toxic tort cases involving plaintiffs allegedly injured by beneze exposure in which evidence of chromosomal aberrations was offered. The judicial decisions in these cases were evaluated to determine whether the judges properly understood and applied the scientific information on biomarkers, and to determine how useful the biomarker data was to the ultimate outcome of the case. A standardized multi-criteria analysis sheet was used to evaluate each case. A total of 17 U.S. court cases decided in the period from 1995 to 2012 that involved benzene chromosomal biomarker evidence were identified and evaluated in this study. The analysis identifies several problems in how judges and juries in these cases dealt with biomarker evidence, including: (i) some courts treat the evidence as deterministic rather than probabilistic, incorrectly concluding that biomarker evidence alone proves or disproves causation, or in other cases holding that the biomarker data is completely irrelevant and thus inadmissible; (ii) different courts treated the same biomarker evidence differently, resulting in inconsistent decisions; and (iii) individual judges made statements in specific cases indicating a poor understanding of biomarkers. Notwithstanding these limitations, the overall results of using chromosomal biomarker evidence in these toxic tort cases was beneficial, as the evidence was instrumental in helping to prove or disprove causation in appropriate cases. This analysis demonstrates that biomarker data can provide effective and useful evidence in toxic tort litigation, and are likely to be used increasingly frequently in such cases. At the same time, the problems identified in this analysis with handling of biomarker data by some courts provide important lessons for judges, attorneys, and scientific experts.

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