Attachment 13rev: Study Organisation and Management

The method validation study was initiated in 2010 by a group of representatives from various metal commodities seeking to standardize fluid compositions and testing protocols for the basic bioelution methods being used across the industry. To investigate the within-lab repeatability and between-lab reproducibility of bioaccessibility testing in different bioelution fluids (including gastric fluid), five laboratories measured metal release from six metal-containing materials following one defined protocol issued by the study sponsors. The study was funded by five commodity groups as listed below, with each organization having a key point person that participated in steering team and technical discussions. An independent third party (study coordinator) was tasked with overseeing the overall study data analysis, publication of results, and applications of learning lessons to the SOP. The statistical analyses were conducted by independent biostatisticians.

Five independent laboratories participated in the study, each with a designated study director(s) as listed below. Samples of each of the six materials (pre-characterized for particle size, metal content, and surface area) were distributed to each of the five laboratories from two independent repositories (Particle Technologies Laboratory (Downers Grove, IL, USA) and Outotec (Finland)). Labs were asked to follow a Standard Operating Procedure (SOP; dated November 2010) provided and discussed prior to study initiation. All fluids and experimental set ups were prepared by each individual laboratory. In brief, test materials were added to simulated bioelution fluids (including gastric fluid) and extracted after 2 hours following the conditions described in the SOP (e.g. pH, temperature). Following a filtration step, extracts were analyzed and the amounts of metals released into solution were reported. Laboratories measured the release of seven different metals (Cr, Co, Cu, Fe, Ni, Pb and Zn) depending on the composition of the test materials. All extractions were prepared and analyzed in triplicate. Each laboratory generated a comprehensive report, which underwent a QA exercise by the study coordinator. A detailed review and comparison between the SOP and the 5 laboratory reports was performed. As part of this review, individual exchanges were held with the labs to address information gaps and confirm data when necessary. Finally, two independent biostatisticians were commissioned to perform statistical analysis of the within-lab repeatability and between-lab reproducibility, as listed below. The outcome of the round robin was published in a peer-reviewed journal (Henderson et al., 2014).

Study Coordinator:
Dr. Rayetta Henderson who had joined ToxStrategies, Inc. (Raleigh, NC, USA) at the time of the report evaluation, statistical analysis phase, and manuscript publication[1].

Study Funding Sponsors and Steering Team Representatives:
1. Eurometaux, Dr. Violaine Verougstraete (Brussels, Belgium)
2. Nickel Producers Environmental Research Association, Inc., Dr. Rayetta Henderson during the round robin study and Dr. Adriana Oller during the manuscript publication phases (Durham, NC, USA)

[1] Dr Verougstraete and Dr. Oller provided acted as advisers to Dr. Henderson.

3. Cobalt Development Institute, Dr. Thomas O. Brock (now at Duke University, Durham, NC, USA) and Dr. Ruth Danzeisen (Umkirch, Germany)
4. European Copper Institute, Dr. Katrien Delbeke (Brussels, Belgium)
5. International Zinc Association, Dr. Frank Van Assche (Brussels, Belgium)

Independent Laboratories and Designated Study Directors:

1. CIMM (Chilean Mining and Metallurgy Research Center, now called CECM), Drs. Patricio Rodriguez and José Arbildua (Santiago, Chile)
2. ECTX bvba, Dr. Tony Brouwers (Hasselt, Belgium)
3. Kirby Memorial Health Center, Ms. Danielle Cappellini (Wilkes-Barre, PA, USA)
4. KTH Royal Institute of Technology, Drs. Inger Odnevall Wallinder and Gunilla Herting (Stockholm, Sweden)
5. Oregon State University, Dr. Kim Anderson (Corvallis, OR, USA)

Independent Biostatisticians:

1. Dr. Peter-Th. Wilrich, professor at Freie Universität Berlin (Berlin, Germany)
2. Dr. Greg Hixon at ToxStrategies, Inc. consulting firm (Austin, Texas, USA)