


NAFTA Technical Working Group on Pesticides
Grupo de Trabajo Técnico del TLCAN sobre Plaguicidas
Le groupe de travail technique de l'ALENA sur les pesticides

PROJECT COMPLETION SHEET

SUBCOMMITTEE: Regulatory Capacity Building

PROJECT TITLE: **Maximum Tolerated Dose (MTD) Harmonization**

PROJECT ID: RC02-98-1205

PROJECT LEADS: Canada: Connie Moase
United States: Jeff Herndon

PROJECT DATES: Initiated June 1998. Completed December 2005.

GOAL/OBJECTIVE: The harmonization of the approaches used in the United States and in Canada for the selection of doses used in carcinogenic bioassays.

BACKGROUND:

The United States Environmental Protection Agency (EPA) and Health Canada's Pest Management Regulatory Agency (PMRA), like regulatory authorities in Europe and Japan, require that the highest dose selected for chronic toxicity or carcinogenicity bioassays should not (with exception of neoplastic development) induce overt (excessive) toxicity or shorten the lifespan of the test animals. However, international and national differences exist in the types and severity of effects that are interpreted as providing evidence of minimal or excessive toxicity. Characterizing the toxicity observed in a completed bioassay is also undertaken to support decisions that the doses used in a study were adequate to assess potential toxicity or carcinogenicity (i.e., a Maximum Tolerated Dose, or MTD, was attained or exceeded). There had been a lack of harmonization of approaches to dose selection for proposed bioassays and evaluation of the adequacy of doses administered in completed studies. As a result of these different views regarding the severity of toxic effects used to provide evidence that a MTD had been attained or exceeded, a completed bioassay could have been considered to be acceptable by one organization but not by another. This project was originally designed to ensure a harmonized approach in the EPA and the PMRA on the appropriateness of doses used for chronic toxicity and carcinogenicity bioassays.

OUTPUT/RESULTS:

The EPA's Health Effects Division and the PMRA jointly developed an interim document intended to supplement and expand on information provided in the EPA draft *Final Carcinogen Risk Assessment Guidelines* (2003) and the International Life Sciences Institute (ILSI) report on *Principles for the Selection of Doses in Chronic Rodent Bioassays* (1997). The ILSI has now undertaken the project, funded in part through a cooperative agreement with the EPA, to update and expand upon the 1997 report and to incorporate many of the elements outlined in the EPA/PMRA interim joint document. It is anticipated that the current ILSI project will result in a peer-reviewed publication that will provide guidance to Industry and Regulators on all aspects of dose selection for chronic bioassays to facilitate appropriate study design. For evaluators, the intent is to provide guidance on the qualitative and quantitative evidence that supports a determination that the doses selected for or used in a chronic rodent bioassay, were adequate, should have been higher, or were excessive to promote consistent and uniform decision-making.