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An Approach to Using Toxicogenomic Data In U.S. EPA Human Health Risk Assessments: A Dibutyl Phthalate Case Study

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LIST OF ABBREVIATIONS AND ACRONYMS

Please note that most gene and protein name abbreviations are not included in this list because of the large number of genes and proteins described in the report. The gene and protein names have been standardized using information from the Rat Genome Project.

ADH alcohol dehydrogenase

ADME absorption, distribution, metabolism, and excretion

AGD anogenital distance

AMH anti-mullerian hormone

ANOVA analysis of variance AR androgen receptor

BBDR biologically based dose-response

BBP butyl benzyl phthalate

BMD benchmark dose

BMDL benchmark dose lower confidence limit

BPA bisphenol A

cDNA complementary DNA

CNPs copy-number polymorphisms

DBP dibutyl phthalate

DEG differentially expressed gene DEHP di-(2-ethylhexyl) phthalate

DEP diethyl phthalate
DMP dimethyl phthalate

DOTP diocytyl tere-phthalate

DPP dipentyl phthalate

EDC endocrine disrupting chemical EPA Environmental Protection Agency

ER estrogen receptor

ESTs expressed sequence tags

FDA Food and Drug Administration

GAPDH glyceraldehyde-3-phosphate dehydrogenase

GD gestation day
GO Gene Ontology
GSH glutathione

LIST OF ABBREVIATIONS AND ACRONYMS (continued)

HESI Health and Environmental Sciences Institute

ILSI International Life Sciences Institute

IPA Ingenuity® Pathway Analysis

IPCS International Programme on Chemical Safety

IRIS Integrated Risk Information System

KEGG Kyoto Encyclopedia of Genes and Genomes

LC Leydig cell

LMW low molecular weight

LOAEL lowest-observed-adverse-effect level

LOEL lowest-observed-effect level

MAPK/ERK mitogen-activated protein kinase/extracellular signal-regulated kinase

MAQC MicroArray Quality Control

MAS microarray suite

MBP monobutylphthalate

MMP matrix metalloproteinase

MOA mode of action mRNA messenger RNA

NCCT National Center for Computational Toxicology NCEA National Center for Environmental Assessment

NIEHS National Institute of Environmental Health Sciences

NOAEL no-observed-adverse-effect level

NOEL no-observed-effect level
NRC National Research Council
NTP National Toxicology Program

PA pathway activity

PBPK physiologically-based pharmacokinetic

PCA principal component analysis
PCR polymerase chain reaction

PFOA perfluorooctanoic acid

PND postnatal day

POD point of departure

PPAR peroxisome proliferator-activated receptor

PPS preputial separation

LIST OF ABBREVIATIONS AND ACRONYMS (continued)

RA risk assessment

RACB reproductive assessment by continuous breeding

RfD reference dose

RT-PCR reverse transcription-polymerase chain reaction

SD Sprague-Dawley SLR signal log ratio

SNPs single nucleotide polymorphisms

SNR signal-to-noise ratio SPC Science Policy Council

STAR Science to Achieve Results

T testosterone

TD toxicodynamics
TF transcription factor

TK toxicokinetics

Tox Review Toxicological Review

UF_H intraspecies uncertainty factor

UMDNJ University of Medicine and Dentistry of New Jersey

VLI valine, leucine, isoleucine

WD Wolffian duct

WOE weight-of-evidence

PREFACE

The U.S. Environmental Protection Agency (EPA) is interested in developing methods to use genomic data most effectively in risk assessments performed at EPA. The National Center for Environmental Assessment (NCEA) within the Office of Research and Development (ORD) prepared this document for the purpose of describing and illustrating an approach for using toxicogenomic data in risk assessment. The approach and dibutyl phthalate (DBP) case study described in this document were developed by a team of scientists at EPA laboratories and centers, and outside organizations including The Hamner Institutes for Health Sciences, the National Institute of Environmental Health Sciences (NIEHS), and the EPA National Center for Environmental Research (NCER) Science to Achieve Results (STAR) Environmental Bioinformatics and Computational Toxicology (Comp Tox) Center at the University of Medicine and Dentistry of New Jersey (UMDNJ) and Rutgers University. The intended audience for this document includes risk assessors as well as scientists with expertise in genomics, bioinformatics, toxicology, and statistics. The approach outlined in this document is expected to be useful to EPA risk assessors in the Integrated Risk Information System (IRIS) Program and other program offices and regions, as well as the scientific community at large. The review of the literature on the use of genomic data in risk assessment, as well as discussions of issues, recommendations, and methods for evaluating and analyzing toxicogenomic data, could be useful to scientists and risk assessors within and outside of EPA. The research needs identified in this document will be useful to scientists performing toxicology and toxicogenomic research studies for application to risk assessment. The DBP case study presented in this document is a separate activity from the IRIS DBP health assessment. The review of the literature included in this document was last updated in July 2007.

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