## ARC MONOGRAPHS

## PERFLUOROOCTANOIC ACID (PFOA) AND PERFLUOROOCTANESULFONIC ACID (PFOS)

THE A P R I

**VOLUME 135** 

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International Agency for Research on Cancer



## **LIST OF ABBREVIATIONS**

| 2-AAF            | 2-acetylaminofluorene                                                 |
|------------------|-----------------------------------------------------------------------|
| ACGIH            | American Conference of Governmental Industrial Hygienists             |
| ACOX             | acyl-coenzyme A oxidase                                               |
| ACS              | American Cancer Society                                               |
| ADME             | absorption, distribution, metabolism, or excretion                    |
| AFB <sub>1</sub> | aflatoxin B <sub>1</sub>                                              |
| AFFF             | aqueous film-forming foam                                             |
| AHR              | aryl hydrocarbon receptor                                             |
| AOR              | adjusted odds ratios                                                  |
| APFO             | ammonium perfluorooctanoate                                           |
| AR               | androgen receptor                                                     |
| ARE              | antioxidant responsive element                                        |
| ASTM             | American Society for Testing and Materials                            |
| ATBC             | Alpha-Tocopherol, Beta-Carotene Cancer Prevention                     |
| ATP              | adenosine triphosphate                                                |
| ATSDR            | Agency for Toxic Substances and Disease Registry                      |
| AUC              | area under the curve                                                  |
| BMI              | body mass index                                                       |
| BrdU             | bromodeoxyuridine                                                     |
| bw               | body weight                                                           |
| cAMP             | cyclic adenosine monophosphate                                        |
| CAR              | constitutive androstane receptor                                      |
| CAT              | catalase                                                              |
| CBD              | cannabidiol                                                           |
| CEPA             | Canadian Environmental Protection Act                                 |
| CERCLA           | Comprehensive Environmental Response, Compensation, and Liability Act |
| CGA              | chlorogenic acid                                                      |
| CHDS             | Child Health and Development Studies                                  |
| СНО              | Chinese hamster ovary                                                 |
| CI               | confidence interval                                                   |
| CIOB             | Chemicals in Our Bodies                                               |
| CNBCSP           | Chinese National Breast Cancer Screening Program                      |
| CoA              | coenzyme A                                                            |
| ConA             | concanavalin A                                                        |

| CONTAMEuropean Food Safety Authority Panel on Contaminants in the Food ChainCpG5'-C-phosphate-G-3'-dinucleotideCPSCancer Prevention StudyCRPC-reactive proteinCScollagen sandwichCTSCalifornia Teachers StudyCVcoefficient of variationCYPcytochrome P450DCF2',7'-dichlorofluoresceinDCF-DA2',7'-dichlorofluorescein diacetateDCFH-DA2',7'-dichlorofluorescein diacetateDENdiethylnitrosamineDFTJDongfeng-TongjidG2'-deoxyguanosineDHEAdehydroepiandrosteronediPAPpolyfluoroalkyl phosophate diesterDMBA7,12-dimethylbenz[a]anthraceneDMRdifferentially methylated region |  |
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| CPSCancer Prevention StudyCRPC-reactive proteinCScollagen sandwichCTSCalifornia Teachers StudyCVcoefficient of variationCYPcytochrome P450DCF2',7'-dichlorofluoresceinDCF-DA2',7'-dichlorofluorescein diacetateDCFH-DA2',7'-dichlorofluorescein diacetateDENdiethylnitrosamineDFTJDongfeng-TongjidG2'-deoxyguanosineDHEAdehydroepiandrosteronediPAPpolyfluoroalkyl phosophate diesterDMBA7,12-dimethylbenz[a]anthracene                                                                                                                                                   |  |
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| diPAPpolyfluoroalkyl phosophate diesterDMBA7,12-dimethylbenz[a]anthracene                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |  |
| DMBA 7,12-dimethylbenz[a]anthracene                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |  |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |  |
| DMR differentially methylated region                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |  |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |  |
| DMSO dimethyl sulfoxide                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |  |
| DNMT DNA methyltransferase                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |  |
| DoD Department of Defense                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |  |
| DoDSR Department of Defense Serum Repository                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |  |
| DOX doxycycline                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |  |
| DTH delayed-type hypersensitivity                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |  |
| EC European Commission                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |  |
| EC <sub>50</sub> half-maximal effective concentration                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |  |
| ECA Environment and Childhood Asthma                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |  |
| ECCC Environment and Climate Change Canada                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |  |
| ECF electrochemical fluorination                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |  |
| ECHA European Chemicals Agency                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |  |
| EFSA European Food Safety Authority                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |  |
| eGFR estimated glomerular filtration rate                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |  |
| ELISA enzyme-linked immunosorbent assay                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |  |
| EPCRA Emergency Planning and Community Right-to-Know Act                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |  |
| ER estrogen receptor                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |  |
| ERS endoplasmic reticulum stress                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |  |
| ESI electrospray ionization                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |  |
| <i>N</i> -EtFOSAA <i>N</i> -ethyl-perfluorooctane sulfonamido acetic acid                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |  |
| EU European Union                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |  |
| EWAS epigenome-wide association analysis study                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |  |
| FDR false discovery rate                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |  |
| FMC Finnish Maternity Cohort                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |  |
| Fpg   formamidopyrimidine-DNA glycosylase                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |  |
| FSANZ Food Standards Australia New Zealand                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |  |
| FT3 free triiodothyronine                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |  |
| FT4 free thyroxine                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |  |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |  |
| FTOH fluorotelomer alcohol                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |  |
| GBCA Genetic and Biomarkers study for Childhood Asthma                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |  |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |  |

| GF               | glomerular function                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| GFR              | glomerular filtration rate                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| GGT              | gamma-glutamyl transferase                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| GJIC             | gap junctional intercellular communication                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| GLP              | Good Laboratory Practice                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| GM               | geometric mean                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| GM-CSF           | granulocyte-macrophage colony-stimulating factor                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| GPx              | glutathione peroxidase                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| GRULAC           | Group of Latin America and the Caribbean                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| GSH              | glutathione                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| GSPE             | grape seed proanthocyanidin extract                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| GSR              | glutathione reductase                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| GSSG             | oxidized glutathione                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| GST              | glutathione S-transferase                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| γH2AX            | phosphorylated H2A histone family member X                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| HBM              | Human Biomonitoring                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| HBM4EU           | Human Biomonitoring for Europe                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| НСС              | hepatocellular carcinoma                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| HETE             | hydroxyeicosatetraenoic acid                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| HFD              | high-fat diet                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| HGF              | hepatocyte growth factor                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| Hib              | Haemophilus influenza type b                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| НИС              | human mast cell                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| HMVEC            | human microvascular endothelial cells                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| HO-1             | haem oxygenase 1                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| HOME             | Health Outcomes and Measures of the Environment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| HPLC             | high-performance liquid chromatography                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| HR               | hazard ratio                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| HUVEC            | human umbilical vein endothelial cell                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| IARC             | International Agency for Research on Cancer                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| IC <sub>50</sub> | half-maximal inhibitory concentration                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| ICC              | intraclass correlation coefficient                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| IFN-γ            | interferon gamma                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| -                | immunoglobulin                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| Ig<br>IKIDS      | Illinois Kids Development Study                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| IL IKIDS         | interleukin                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| INHAND           | International Harmonization of Nomenclature and Diagnostic Criteria for Lesions in Rats and Mice                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| iNOS             | inducible nitric oxide synthase                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| INSR             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|                  | insulin receptor<br>intraperitoneal                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| i.p.<br>IQR      | interquartile range                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|                  | incidence rate ratio                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| IRR              | isofuran                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| IsoF             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| IsoP             | isoprostane                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| ITRC             | Interstate Technology and Regulatory Council                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| i.v.             | intravenous<br>internet and the second s |
| JEM              | job-exposure matrix                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| KC               | key characteristic of carcinogens                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| KEEP             | Korean Elderly Environmental Panel                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| KLH              | keyhole limpet haemocyanin                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |

| LC <sub>50</sub>      | median lethal concentration                                   |
|-----------------------|---------------------------------------------------------------|
| LC-MS/MS              | liquid chromatography-tandem mass spectrometry                |
| L-FABP                | liver fatty acid-binding protein                              |
| LH                    | luteinizing hormone                                           |
| LINE-1                | long interspersed nuclear element 1                           |
| LLE                   | liquid-liquid extraction                                      |
| LMIC                  | low- or middle-income country                                 |
| LOD                   | limit of detection                                            |
| LOQ                   | limit of quantification                                       |
| LOX                   | lipoxygenase                                                  |
| LPS                   | lipopolysaccharide                                            |
| LRTI                  | lower respiratory tract infection                             |
| LTL                   | leukocyte telomere length                                     |
| LWBC                  | Laizhou Wan (Bay) birth cohort                                |
| MCP-1                 | monocyte chemoattractant protein                              |
| MDA                   | malondialdehyde                                               |
| MDL                   | method detection limit                                        |
| MEC                   | Multiethnic Cohort                                            |
| МНС                   | major histocompatibility complex                              |
| miRNA                 | microRNA                                                      |
| mRNA                  | messenger RNA                                                 |
| MLQ                   | method limit of quantification                                |
| MNNG                  | N-methyl-N'-nitro-N-nitrosoguanidine                          |
| MRL                   | minimum reporting level                                       |
| MRP                   | multidrug resistance protein                                  |
| MS                    | mass spectrometry                                             |
| MS/MS                 | tandem mass spectrometry                                      |
| MTT                   | 3-[4,5-dimethylthiazol-2-yl]-2,5 diphenyl tetrazolium bromide |
| NAC                   | N-acetylcysteine                                              |
| NADPH                 | nicotinamide adenine dinucleotide phosphate                   |
| NAFLD                 | non-alcoholic fatty liver disease                             |
| NAR                   | naringin; 4',5,7-trihydroxyflavonone-7-rhamnoglucoside        |
| NASEM                 | National Academies of Sciences, Engineering, and Medicine     |
| NDAA                  | National Defense Authorization Act                            |
| NDI                   | National Death Index                                          |
| NESHAP                | National Emissions Standards for Hazardous Air Pollutants     |
| NeuroP                | neuroprostane                                                 |
| NGF                   | nerve growth factor                                           |
| NHANES                | National Health and Nutrition Examination Survey              |
| NHL                   | non-Hodgkin lymphoma                                          |
| NHMRC                 | National Health and Medical Research Council                  |
| NICHD                 | National Institute of Child Health and Human Development      |
| NK                    | natural killer                                                |
| NO                    | nitric oxide                                                  |
| NOx                   | nitrogen oxides                                               |
| 8-NO <sub>2</sub> Gua | 8-nitrosoguanine                                              |
| NOAEL                 | no observed adverse effect level                              |
| NPDES                 | National Pollutant Discharge Elimination System               |
| NTCP                  | Na+/taurocholate cotransporting polypeptide                   |
| NTP                   | National Toxicology Program                                   |
|                       |                                                               |

| OAT               | organic acid transporter                                             |
|-------------------|----------------------------------------------------------------------|
| OATP              | organic anion transporting polypeptide                               |
| OCC               | Odense Child Cohort                                                  |
| ОСМ               | organotypic culture model                                            |
| 8-OHdG            | 8-hydroxy-2'-deoxyguanosine                                          |
| OR                | odds ratio                                                           |
| 8-oxodG           | 8-oxo-2'-deoxyguanosine                                              |
| РАН               | polycyclic aromatic hydrocarbon                                      |
| PanIN             | pancreatic intraepithelial neoplasia                                 |
| PBDE              | polybrominated diphenyl ether                                        |
| РВМС              | peripheral blood mononuclear cells                                   |
| РВРК              | physiologically based pharmacokinetic                                |
| РСВ               | polychlorinated biphenyl                                             |
| PCDD              | 2,3,7,8-substituted polychlorinated dibenzodioxin                    |
| PCDF              | 2,3,7,8-substituted polychlorinated dibenzofuran                     |
| PCNA              | proliferating cell nuclear antigen                                   |
| РСО               | palmitoyl coenzyme A oxidase                                         |
| PCR               | polymerase chain reaction                                            |
| PFAA              | perfluoroalkyl acid                                                  |
| PFAS              | perfluoroalkyl and polyfluoroalkyl substances                        |
| PFHpS             | perfluoroheptane sulfonate                                           |
| PFHxS             | perfluorohexanesulfonic acid                                         |
| PFNA              | perfluorononanoic acid                                               |
| PFOA              | perfluorooctanoic acid                                               |
| PFOS              | perfluorooctanesulfonic acid                                         |
| PGF               | prostaglandin                                                        |
| PHA               | phytohaemagglutinin                                                  |
| РКА               | protein kinase A                                                     |
| РКС               | protein kinase C                                                     |
| PLCO              | Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial       |
| РМ                | particulate matter                                                   |
| PM <sub>2.5</sub> | particulate matter with diameter < 2.5 μm                            |
| РОР               | persistent organic pollutant                                         |
| POSF              | perfluorooctane sulfonyl fluoride                                    |
| PPAR              | peroxisome proliferator-activated receptor                           |
| ppb               | parts per billion                                                    |
| PPE               | personal protective equipment                                        |
| ppm               | parts per million                                                    |
| PR                | progesterone receptor                                                |
| PTFE              | polytetrafluoroethylene                                              |
| PUF               | polyurethane foam                                                    |
| PWS               | public water systems                                                 |
| PXR               | pregnane X receptor                                                  |
| qPCR              | quantitative polymerase chain reaction                               |
| QuEChERS          | quick, easy, cheap, effective, rugged, safe                          |
| RACK-1            | receptor for activated C kinase 1                                    |
| RBC               | red blood cell                                                       |
| RCC               | renal cell carcinoma                                                 |
| RD                | human embryonal rhabdomyosarcoma cell line                           |
| REACH             | Registration, Evaluation, Authorisation and Restriction of Chemicals |
|                   |                                                                      |

| RL        | reporting limit                                                       |
|-----------|-----------------------------------------------------------------------|
| RNA       | ribonucleic acid                                                      |
| tRNA      | transfer RNA                                                          |
| RNS       | reactive nitrogen species                                             |
| ROS       | reactive oxygen species                                               |
| RONS      | reactive oxygen and nitrogen species                                  |
| RPE       | retinal pigment epithelial                                            |
| RR        | rate ratio                                                            |
| RT-PCR    | reverse transcription-polymerase chain reaction                       |
| RSV       | respiratory syncytial virus                                           |
| SCAP      | sterol regulatory element-binding protein cleavage-activating protein |
| SD        | standard deviation                                                    |
| SEER      | Surveillance, Epidemiology, and End Results                           |
| SEM       | systemic evidence map                                                 |
| SHBG      | sex hormone-binding globulin                                          |
| SIR       | standardized incidence ratio                                          |
| SMBCS     | Sheyang Mini Birth Cohort Study                                       |
| SMR       | standardized mortality ratio                                          |
| SNUR      | Significant New Use Rules                                             |
| SOD       | superoxide dismutase                                                  |
| SPE       | solid-phase extraction                                                |
| SRBC      | sheep red blood cell                                                  |
| StAR      | steroidogenic acute regulatory                                        |
| STEL      | short-term exposure limit                                             |
| $T_{1/2}$ | half-life                                                             |
| TAC       | total antioxidant capacity                                            |
| TAD       | total administered dose                                               |
| TBARS     | thiobarbituric acid-reactive substance                                |
| ТСА       | tricarboxylic acid                                                    |
| TCDD      | 2,3,7,8-tetrachlorodibenzo- <i>p</i> -dioxin                          |
| TCR       | T-cell receptor                                                       |
| TDAR      | T-cell-dependent antibody response                                    |
| TDI       | tolerable daily intake                                                |
| TFE       | tetrafluoroethylene                                                   |
| TGCT      | testicular germ cell tumour                                           |
| TH        | thyroid hormone                                                       |
| ТК        | toxicokinetic                                                         |
| TL        | telomere length                                                       |
| TNF-α     | tumour necrosis factor alpha                                          |
| TNP       | trinitrophenyl                                                        |
| TPOAb     | thyroid peroxidase antibody                                           |
| TR        | thyroid hormone receptor                                              |
| TRI       | Toxics Release Inventory                                              |
| TSH       | thyroid-stimulating hormone                                           |
| TSCA      | Toxic Substances Control Act                                          |
| TT3       | total triiodothyronine                                                |
| TT4       | total thyroxine                                                       |
| TTR       | transthyretin                                                         |
| TWA       | time-weighted average                                                 |
| TWI       | tolerable weekly intake                                               |
|           |                                                                       |

| UBA        | Umweltbundesamt (German Environment Agency)   |
|------------|-----------------------------------------------|
| UCMR 3     | Third Unregulated Contaminant Monitoring Rule |
| UK         | United Kingdom                                |
| UNEP       | United Nations Environment Programme          |
| UPR        | unfolded protein response                     |
| US         | United States                                 |
| USA        | United States of America                      |
| US EPA     | United States Environmental Protection Agency |
| US FDA     | United States Food and Drug Administration    |
| $V_{ m d}$ | volume of distribution                        |
| vP         | very persistent                               |
| WBC        | white blood cell                              |
| WT         | wildtype                                      |