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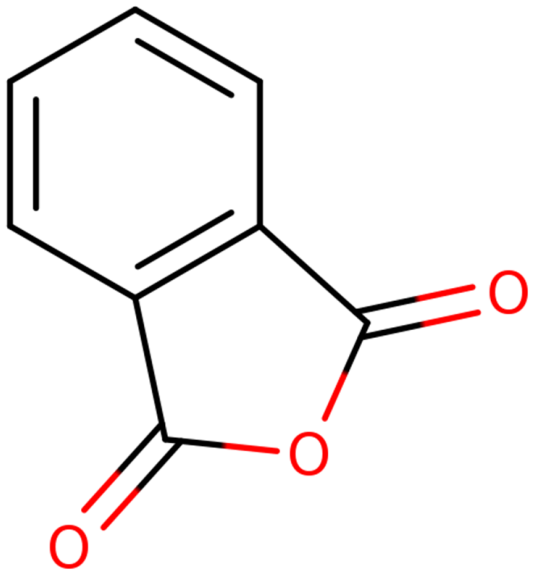
Office of Chemical Safety and
Pollution Prevention

Data Extraction Information for Environmental Hazard and Human Health Hazard Animal Toxicology and Epidemiology for Phthalic Anhydride

Systematic Review Support Document for the Draft Risk Evaluation

CASRN: 85-44-9



March 2026

This supplemental file contains information regarding the data extraction results relevant to the *Draft Environmental Hazard Assessment for Phthalic Anhydride* and the *Draft Human Health Hazard Assessment for Phthalic Anhydride*. For the data extraction, EPA used the TSCA systematic review process described in the *Draft Systematic Review Protocol Supporting TSCA Risk Evaluations for Chemical Substances* (also referred to as the '2021 Draft Systematic Review Protocol'). Any updated steps in the systematic review process for data extraction since the publication of the 2021 Draft Systematic Review Protocol are described in the *Draft Systematic Review Protocol for Phthalic Anhydride*. EPA conducted data extraction based on author-reported descriptions and results; additional analyses (*e.g.*, statistical analyses performed during data integration into the risk evaluation) potentially conducted by EPA are not contained in this supplemental file.

Environmental Hazard Data Extraction: As explained in Section 6.4 of the 2021 Draft Systematic Review Protocol, key study details (*e.g.*, exposure duration vs. study duration) were extracted from references that underwent data quality evaluation; these study details are available in the tables below. The study details and respective endpoints were organized by first the chemical (target chemical followed by analog chemical), then relevant habitat (*i.e.*, aquatic vs. terrestrial), followed by taxa categories (*e.g.*, vertebrates, invertebrates, vegetation), taxonomic groups (*e.g.*, fish, amphibian, mammalian, avian, worms, vascular plants), individual species, and finally exposure duration.

All the references that underwent data quality evaluation using the environmental hazard data quality metrics were extracted regardless of metric ranking and are included in this supplemental file. In the environmental hazard data extraction table, for some studies there were hazard health outcomes with multiple health effect levels extracted from ECOTOX; if all the data for one same health outcome were the same except for the health effect level (*e.g.*, LOEL level), multiple data extraction rows were combined into a single row in the table. All the extracted environmental hazard data will also be available in the ECOTOXicology Knowledgebase (ECOTOX) database; moreover, additional data sources and experimental details for these studies will also be available in ECOTOX.

Data Extraction of Rodent Data for the Application of Environmental Hazard: For phthalic anhydride, toxicity data gaps were identified for mammalian wildlife relevant to the terrestrial compartment of the environmental hazard assessment. This table includes rodent data for phthalic anhydride, which were used as proxy for mammalian wildlife. The rodent data were evaluated following the human health hazard animal toxicity evaluation and extraction process; however, additional data for health outcomes most relevant for environmental hazard assessment were also extracted and are listed here.

Human Health Hazard Animal Toxicity Extraction: This supplemental file contains data extraction information for key references identified by EPA as described in the *Draft Systematic Review Protocol for Phthalic Anhydride*. Data from references that were within an order of magnitude of the existing assessment HED were extracted and detailed data were extracted from each individual health outcome within each organ/system. Any co-critical effects were reported along with OQD for the health outcome. A detailed summary statement of each study is reported along with the major limitations as identified by the reviewer and any guidelines used.

Epidemiological Study Information Extraction: All epidemiology references that met PECO screening criteria and further filtering criteria and had an overall quality determination of High, Medium, or Low were extracted as detailed in Section 6.4 of the 2021 Draft Systematic Review Protocol and the *Draft Systematic Review Protocol for Phthalic Anhydride*. The data extracted include the measured health effect or endpoint, a description of the study population, the specific exposure compound measured and summary levels of exposure, the method of exposure measurement, and a summary of the results. Each health outcome assessed in a reference is extracted separately, and as such, each reference may have more than one record in the data extraction tables, with each record categorized by health outcome.

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5177984 Bae, C. J., Lee, J. W., Shim, S. B., Jee, S. W., Lee, S. H., Woo, J. M., Lee, C. K., Hwang, D. Y. (2011). GATA binding protein 3 overexpression and suppression significantly contribute to the regulation of allergic skin inflammation. International Journal of Molecular Medicine 28(2):171-179. **47**

83939 Ban, M., Hettich, D. (2005). Effect of Th2 cytokine antagonist treatments on chemical-induced allergic response in mice. Journal of Applied Toxicology 25(3):239-247. **48**

5353562 Basketter, D. A., Scholes, E. W. (1992). Comparison of the local lymph node assay with the guinea-pig maximization test for the detection of a range of contact allergens. Food and Chemical Toxicology 30(1):65-69. **48**

5177112 Botham, P., Urtizberea, M., Wiemann, C., Manciaux, X., Tilbury, L., Vohr, H. W., Allen, S., Carmichael, N. G., Jouffrey, De, S. (2005). A comparative study of the sensitivity of the 3-induction and 9-induction Buehler test procedures for assessing skin sensitisation potential. Food and Chemical Toxicology 43(1):65-75. **49**

790543 Ema, M., Miyawaki, E., Harazono, A., Kawashima, K. (1997). Developmental toxicity evaluation of phthalic acid, one of the metabolites of phthalic acid esters, in rats. Toxicology Letters 2(3):109-115. **50**

1940789 Fukuyama, T., Tajima, Y., Ueda, H., Hayashi, K., Shutoh, Y., Harada, T., Kosaka, T. (2010). A method for measuring mouse respiratory allergic reaction to low-dose chemical exposure to allergens: an environmental chemical of uncertain allergenicity, a typical contact allergen and a non-sensitizing irritant. Toxicology Letters 195(1):35-43. **51**

12980190 IIT Research Institute, (1996). Respiratory sensitization study of phthalic anhydride (PA): A research project [redacted]. **51**

1336719 Jha, A. M., Singh, A. C., Bharti, M. (1998). Germ cell mutagenicity of phthalic acid in mice. Mutation Research 422(2):207-212. **52**

792143 Kwack, S. J., Han, E. Y., Park, J. S., Bae, J. Y., Ahn, I. Y., Lim, S. K., Kim, D. H., Jang, D. E., Choi, L., Lim, H. J., Kim, T. H., Patra, N., Park, K. L., Kim, H. S., Lee, B. M. (2010). Comparison of the short term toxicity of phthalate diesters and monoesters in Sprague-Dawley male rats. Toxicological Research 26(1):75-82. **53**

697382 Kwack, S., Kim, K., Kim, H., Lee, B. (2009). Comparative toxicological evaluation of phthalate diesters and metabolites in Sprague-Dawley male rats for risk assessment. Journal of Toxicology and Environmental Health, Part A: Current Issues 72(21-22):1446-1454. **54**

699519 Lake, B., Gangolli, S., Grasso, P., Lloyd, A. (1975). Studies on the hepatic effects of orally administered di-(2-ethylhexyl) phthalate in the rat. Toxicology and Applied Pharmacology 32(2):355-367. **54**

61572 Oishi, S., Hiraga, K. (1980). Testicular atrophy induced by phthalic acid esters: Effect on testosterone and zinc concentrations. Toxicology and Applied Pharmacology 53(1):35-41. **55**

65818 Sarlo, K., Clark, E. D. (1992). A tier approach for evaluating the respiratory allergenicity of low molecular weight chemicals. Toxicological Sciences 18(1):107-114. **55**

62970 Sarlo, K., Clark, E. D., Ferguson, J., Zeiss, C. R., Hatoum, N. (1994). Induction of type I hypersensitivity in guinea pigs after inhalation of phthalic anhydride. Journal of Allergy and Clinical Immunology 94(4):747-756. **56**

5179546 Sung, J. E., Kim, J. E., Go, J., Koh, E. K., Song, S. H., Lee, H. A., Hwang, D. Y. (2016). Age-related response of IL-4/Luc/CNS-1 transgenic mice to phthalic anhydride exposure. Archives of Biological Sciences 68(1):145-154. **56**

5160984 Vandebriel, R. J., Jong, De, W. H., Spiekstra, S. W., Dijk, Van, M., Fluitman, A., Garssen, J., Loveren, Van, H. (2000). Assessment of preferential T-helper 1 or T-helper 2 induction by low molecular weight compounds using the local lymph node assay in conjunction with RT-PCR and ELISA for interferon-gamma and interleukin-4. Toxicology and Applied Pharmacology 162(2):77-85. **57**

Subchronic (>30-91 days)

5180411 Biagnini, R. E., Bernstein, D. I., Gallagher, J. S., Moorman, W. J., Knecht, E. A., Smallwood, A. W., Bernstein, I. L. (1988). Immune-responses of cynomolgus monkeys to phthalic-anhydride. Journal of Allergy and Clinical Immunology 82(1):23-29. **62**

63768 NCI, (1979). Bioassay of phthalic anhydride for possible carcinogenicity. **62**

Chronic (>91 days)

Terrestrial: Avian Extraction Table

CASRN	Exposure and Overall Duration	Test Organism Species, Age, Sex, Source	Exposure Media, Route Grouping, Type, Sample Number	Test Analysis Exposure Parameters	Dose/ Concentration for Each Main Group of the Study	Health Effect as reported by the Study Author(s)	Effect Level as reported by the Study Author(s)*	Health Outcome Identified by the Assessor	Overall Quality Determination	HERO ID
85-44-9	<2 Day(s), (11 Day(s))	*Gallus gallus* (Chicken), Embryo, 3 Day(s), Not Reported, Laboratory (OBTAINED FROM THE HATCHERY OF SIIPIKARJANHOITAJAIN LIITTO RY, HAMEENLINNA, FINLAND)	No substrate, Injection, Injection, unspecified, Not Reported	Unmeasured	0 umol/org / 0.17 umol/org / 0.34 umol/org / 0.68 umol/org / 1.4 umol/org	Mortality (Mortality-Mortality, Response Site: Not reported)	LD50 (0.56 umol/org); NR-ZERO (0.17 umol/org)	Mortality	Medium	94541
85-44-9	<2 Day(s), (11 Day(s))	*Gallus gallus* (Chicken), Embryo, 3 Day(s), Not Reported, Laboratory (OBTAINED FROM THE HATCHERY OF SIIPIKARJANHOITAJAIN LIITTO RY, HAMEENLINNA, FINLAND)	No substrate, Injection, Injection, unspecified, Not Reported	Unmeasured	0 umol/org / 0.17 umol/org / 0.34 umol/org / 0.68 umol/org / 1.4 umol/org	Mortality (Mortality-Mortality, Response Site: Not reported)	LD50 (0.56 umol/org); NR-ZERO (0.17 umol/org)	Mortality	Medium	94541
85-44-9	11 Day(s), (11 Day(s))	*Gallus gallus* (Chicken), Embryo, 3 Day(s), Not Reported, Laboratory (OBTAINED FROM THE HATCHERY OF SIIPIKARJANHOITAJAIN LIITTO RY, HAMEENLINNA, FINLAND)	No substrate, Injection, Injection, unspecified, Not Reported	Unmeasured	0 umol/org / 0.17 umol/org / 0.34 umol/org / 0.68 umol/org / 1.4 umol/org	Growth (Development-Deformation, Response Site: Not reported)	ED50 (0.38 umol/org)	Development/Growth	Medium	94541

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Terrestrial: Avian Extraction Table

CASRN	Exposure and Overall Duration	Test Organism Species, Age, Sex, Source	Exposure Media, Route Grouping, Type, Sample Number	Test Analysis Exposure Parameters	Dose/ Concentration for Each Main Group of the Study	Health Effect as reported by the Study Author(s)	Effect Level as reported by the Study Author(s)*	Health Outcome Identified by the Assessor	Overall Quality Determination	HERO ID
85-44-9	11 Day(s), (11 Day(s))	*Gallus gallus* (Chicken), Embryo, 3 Day(s), Not Reported, Laboratory (OBTAINED FROM THE HATCHERY OF SIIPIKARJANHOITAJAIN LIITTO RY, HAMEENLINNA, FINLAND)	No substrate, Injection, Injection, unspecified, Not Reported	Unmeasured	0 umol/org / 0.17 umol/org / 0.34 umol/org / 0.68 umol/org / 1.4 umol/org	Mortality (Mortality-Mortality, Response Site: Not reported)	LD50 (0.55 umol/org); NR-ZERO (1.4 umol/org); NR-ZERO (0.17 umol/org)	Mortality	Medium	94541
85-44-9	11 Day(s), (11 Day(s))	*Gallus gallus* (Chicken), Embryo, 3 Day(s), Not Reported, Laboratory (OBTAINED FROM THE HATCHERY OF SIIPIKARJANHOITAJAIN LIITTO RY, HAMEENLINNA, FINLAND)	No substrate, Injection, Injection, unspecified, Not Reported	Unmeasured	0 umol/org / 0.17 umol/org / 0.34 umol/org / 0.68 umol/org / 1.4 umol/org	Growth (Development-Deformation, Response Site: Not reported)	ED50 (0.38 umol/org)	Development/Growth	Medium	94541
85-44-9	11 Day(s), (11 Day(s))	*Gallus gallus* (Chicken), Embryo, 3 Day(s), Not Reported, Laboratory (OBTAINED FROM THE HATCHERY OF SIIPIKARJANHOITAJAIN LIITTO RY, HAMEENLINNA, FINLAND)	No substrate, Injection, Injection, unspecified, Not Reported	Unmeasured	0 umol/org / 0.17 umol/org / 0.34 umol/org / 0.68 umol/org / 1.4 umol/org	Mortality (Mortality-Mortality, Response Site: Not reported)	LD50 (0.55 umol/org); NR-ZERO (1.4 umol/org); NR-ZERO (0.17 umol/org)	Mortality	Medium	94541

* If multiple extractions contained all identical information except the effect level, extraction rows were collapsed and the differing levels are listed by comma in this row.

Aquatic: Fish Extraction Table

CASRN	Exposure and Overall Duration	Test Organism Species, Age, Sex, Source	Exposure Media, Route Grouping, Type, Sample Number	Test Analysis Exposure Parameters	Dose/ Concentration for Each Main Group of the Study	Health Effect as reported by the Study Author(s)	Effect Level as reported by the Study Author(s)*	Health Outcome Identified by the Assessor	Overall Quality Determination	HERO ID
85-44-9	7 Day(s), (7 Day(s))	*Danio rerio* (Zebra Danio), Blastula, 2-4 hours post-spawn, Not Reported, Laboratory (OBTAINED FROM AUTHOR'S OWN LABORATORY CULTURE)	Fresh water, Aqueous (aquatic habitat), Renewal, Not Reported	Unmeasured	Not Coded	Mortality (Mortality-Mortality, Response Site: Not reported)	LC50 (560 (320-1000) mg/L); LOEC (1000 mg/L)	Mortality	Medium	5353166
85-44-9	7 Day(s), (7 Day(s))	*Danio rerio* (Zebra Danio), Blastula, 2-4 hours post-spawn, Not Reported, Laboratory (OBTAINED FROM AUTHOR'S OWN LABORATORY CULTURE)	Fresh water, Aqueous (aquatic habitat), Renewal, Not Reported	Unmeasured	Not Coded	Growth (Development-Teratogenic measurements, Response Site: Not reported)	EC50 (561 (320-1000) mg/L); LOEC (1000 mg/L)	Development/Growth	Medium	5353166
85-44-9	60 Day(s), (60 Day(s))	*Oncorhynchus mykiss* (Rainbow Trout), Egg, 3 Hours post fertilization, Not Reported, Laboratory (FISH HATCHERY AT VAASEN (GELDERLAND, THE NETHERALNDS))	Fresh water, Aqueous (aquatic habitat), Renewal, Not Reported	Unmeasured	Not Coded	Mortality (Mortality-Mortality, Response Site: Not reported)	LC50 (44.2 (40.4-48.3) mg/L); LOEC (32 mg/L)	Mortality	Medium	5353166
85-44-9	60 Day(s), (60 Day(s))	*Oncorhynchus mykiss* (Rainbow Trout), Egg, 3 Hours post fertilization, Not Reported, Laboratory (FISH HATCHERY AT VAASEN (GELDERLAND, THE NETHERALNDS))	Fresh water, Aqueous (aquatic habitat), Renewal, Not Reported	Unmeasured	Not Coded	Growth (Development-Teratogenic measurements, Response Site: Not reported)	EC50 (44.1 (40.1-48.5) mg/L); LOEC (32 mg/L)	Development/Growth	Medium	5353166

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Aquatic: Fish Extraction Table

CASRN	Exposure and Overall Duration	Test Organism Species, Age, Sex, Source	Exposure Media, Route Grouping, Type, Sample Number	Test Analysis Exposure Parameters	Dose/ Concentration for Each Main Group of the Study	Health Effect as reported by the Study Author(s)	Effect Level as reported by the Study Author(s)*	Health Outcome Identified by the Assessor	Overall Quality Determination	HERO ID
85-44-9	60 Day(s), (60 Day(s))	*Oncorhynchus mykiss* (Rainbow Trout), Egg, 3 Hours post fertilization, Not Reported, Laboratory (FISH HATCHERY AT VAASEN (GELDERLAND, THE NETHERALNDS))	Fresh water, Aqueous (aquatic habitat), Renewal, Not Reported	Unmeasured	Not Coded	Growth (Growth-Length, Response Site: Whole organism)	LOEC (32 mg/L)	Development/Growth	Medium	5353166
85-44-9	60 Day(s), (60 Day(s))	*Oncorhynchus mykiss* (Rainbow Trout), Egg, 3 Hours post fertilization, Not Reported, Laboratory (FISH HATCHERY AT VAASEN (GELDERLAND, THE NETHERALNDS))	Fresh water, Aqueous (aquatic habitat), Renewal, Not Reported	Unmeasured	Not Coded	Growth (Growth-Weight, Response Site: Whole organism)	LOEC (32 mg/L)	Development/Growth	Medium	5353166

* If multiple extractions contained all identical information except the effect level, extraction rows were collapsed and the differing levels are listed by comma in this row.

CBI Claimed: CBI Claimed Extraction Table

CASRN	Exposure and Overall Duration	Test Organism Species, Age, Sex, Source	Exposure Media, Route Grouping, Type, Sample Number	Test Analysis Exposure Parameters	Dose/ Concentration for Each Main Group of the Study	Health Effect as reported by the Study Author(s)	Effect Level as reported by the Study Author(s)*	Health Outcome Identified by the Assessor	Overall Quality Determination	HERO ID
85-44-9	CBI Claimed, (CBI Claimed)	CBI Claimed, CBI Claimed, CBI Claimed, CBI Claimed	CBI Claimed, CBI Claimed, CBI Claimed, CBI Claimed	CBI Claimed	CBI Claimed	CBI Claimed	CBI Claimed	Other (please specify below)	High	11138764

* If multiple extractions contained all identical information except the effect level, extraction rows were collapsed and the differing levels are listed by comma in this row.

Aquatic: Non-vascular plants Extraction Table

CASRN	Exposure and Overall Duration	Test Organism Species, Age, Sex, Source	Exposure Media, Route Grouping, Type, Sample Number	Test Analysis Exposure Parameters	Dose/ Concentration for Each Main Group of the Study	Health Effect as reported by the Study Author(s)	Effect Level as reported by the Study Author(s)*	Health Outcome Identified by the Assessor	Overall Quality Determination	HERO ID
88-99-3	72 Hour(s), (72 Hour(s))	*Desmodesmus subspicatus* (Green Algae), Exponential growth phase (log), Not Reported, Laboratory (FROM THE COLLECTION OF ALGAL CULTURES OF THE INSTITUTE OF PLANT PHYSIOLOGY AT THE UNIVERSITY OF GOTTINGEN, GERMANY)	Fresh water, Aqueous (aquatic habitat), Static, Not Reported	Chemical analysis reported	0 mg/L / 100 mg/L	Population (Population-Population growth rate, Response Site: Not reported)	NR (>=100 mg/L)	Development/Growth	High	5353164
88-99-3	72 Hour(s), (72 Hour(s))	*Desmodesmus subspicatus* (Green Algae), Exponential growth phase (log), Not Reported, Laboratory (FROM THE COLLECTION OF ALGAL CULTURES OF THE INSTITUTE OF PLANT PHYSIOLOGY AT THE UNIVERSITY OF GOTTINGEN, GERMANY)	Fresh water, Aqueous (aquatic habitat), Static, Not Reported	Chemical analysis reported	0 mg/L / 100 mg/L	Population (Population-Population growth rate, Response Site: Not reported)	NOEC (>=100 mg/L); EC0 (>=100 mg/L)	Development/Growth	High	5353164
15968-01-1	96 Hour(s), (96 Hour(s))	*Karenia brevis* (Dinoflagellate), Exponential growth phase (log), Not Reported, Laboratory	Salt water, Aqueous (aquatic habitat), Not reported, Not Reported	Unmeasured	0 ppm / 1 ppm / 10 ppm / 20 ppm / 50 ppm / 100 ppm / 200 ppm / 500 ppm / 1000 ppm	Population (Population-Abundance, Response Site: Not reported)	NR (1-1000 ppm)	Development/Growth	Uninformative	790296

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Aquatic: Non-vascular plants Extraction Table

CASRN	Exposure and Overall Duration	Test Organism Species, Age, Sex, Source	Exposure Media, Route Grouping, Type, Sample Number	Test Analysis Exposure Parameters	Dose/ Concentration for Each Main Group of the Study	Health Effect as reported by the Study Author(s)	Effect Level as reported by the Study Author(s)*	Health Outcome Identified by the Assessor	Overall Quality Determination	HERO ID
88-99-3	72 Hour(s), (72 Hour(s))	*Raphidocelis subcapitata* (Green Algae), Exponential growth phase (log), Not Reported, Laboratory	Fresh water, Aqueous (aquatic habitat), Not reported, Not Reported	Chemical analysis reported	Not Coded	Population (Population-Population growth rate, Response Site: Not reported)	EC50 (2270 (1683-3153) mg/L); EC10 (592 (332-1090) mg/L)	Development/Growth	High	789536

* If multiple extractions contained all identical information except the effect level, extraction rows were collapsed and the differing levels are listed by comma in this row.

Aquatic: Arthropods Extraction Table

CASRN	Exposure and Overall Duration	Test Organism Species, Age, Sex, Source	Exposure Media, Route Grouping, Type, Sample Number	Test Analysis Exposure Parameters	Dose/ Concentration for Each Main Group of the Study	Health Effect as reported by the Study Author(s)	Effect Level as reported by the Study Author(s)*	Health Outcome Identified by the Assessor	Overall Quality Determination	HERO ID
88-99-3	48 Hour(s), (48 Hour(s))	*Chironomus plumosus* (Midge), Larva, 3-4 Instar, Not Reported, Laboratory (CULTURES MAINTAINED AT THE CNFRL, COLUMBIA, MO)	Fresh water, Aqueous (aquatic habitat), Static, 10 Organism	Unmeasured	Not Coded	Physiology (Intoxication-Immobile, Response Site: Not reported)	EC50 (>72 mg/L)	Immobilization	Uninformative	1332972
88-99-3	48 Hour(s), (48 Hour(s))	*Chironomus plumosus* (Midge), Larva, 3-4 Instar, Not Reported, Laboratory (CULTURES MAINTAINED AT THE CNFRL, COLUMBIA, MO)	Fresh water, Aqueous (aquatic habitat), Static, 10 Organism	Unmeasured	Not Coded	Mortality (Mortality-Mortality, Response Site: Not reported)	LC50 (>72 mg/L)	Mortality	Uninformative	1332972
88-99-3	24 Hour(s), (48 Hour(s))	*Daphnia magna* (Water Flea), <24 Hour(s), Not Reported, Laboratory	Fresh water, Aqueous (aquatic habitat), Not reported, Not Reported	Chemical analysis reported	Not Coded	Physiology (Intoxication-Immobile, Response Site: Not reported)	EC50 (121 (103-141) mg/L); EC10 (32.6 (4.02-52.8) mg/L)	Immobilization	High	789536
88-99-3	48 Hour(s), (48 Hour(s))	*Daphnia magna* (Water Flea), <24 Hour(s), Not Reported, Laboratory	Fresh water, Aqueous (aquatic habitat), Not reported, Not Reported	Chemical analysis reported	Not Coded	Physiology (Intoxication-Immobile, Response Site: Not reported)	EC10 (6.04 mg/L); EC50 (103 (85.0-123) mg/L)	Immobilization	High	789536

* If multiple extractions contained all identical information except the effect level, extraction rows were collapsed and the differing levels are listed by comma in this row.

Terrestrial: Vascular plants Extraction Table

CASRN	Exposure and Overall Duration	Test Organism Species, Age, Sex, Source	Exposure Media, Route Grouping, Type, Sample Number	Test Analysis Exposure Parameters	Dose/ Concentration for Each Main Group of the Study	Health Effect as reported by the Study Author(s)	Effect Level as reported by the Study Author(s)*	Health Outcome Identified by the Assessor	Overall Quality Determination	HERO ID
88-99-3	75 Day(s), (75 Day(s))	*Lilium davidii* (Lily), Not reported, Not Reported, Laboratory (LILY DEALERS (XIGUOYUAN OF LANZHOU CITY, GANSU PROVINCE, CHINA))	Natural soil, Environmental, Direct application, Not Reported	Unmeasured	0 umol/g soil / 0.01 umol/g soil / 0.05 umol/g soil / 0.25 umol/g soil / 0.5 umol/g soil / 1 umol/g soil	Biochemical (Enzyme(s)-Superoxide dismutase (SOD) enzyme activity, Response Site: Root)	NOEL (0.5 umol/g soil); LOEL (1 umol/g soil)	Mechanistic: Oxidative stress (including redox biology); Photosynthesis	Medium	6824698
88-99-3	75 Day(s), (75 Day(s))	*Lilium davidii* (Lily), Not reported, Not Reported, Laboratory (LILY DEALERS (XIGUOYUAN OF LANZHOU CITY, GANSU PROVINCE, CHINA))	Natural soil, Environmental, Direct application, Not Reported	Unmeasured	0 umol/g soil / 0.01 umol/g soil / 0.05 umol/g soil / 0.25 umol/g soil / 0.5 umol/g soil / 1 umol/g soil	Growth (Growth-Height, Response Site: Shoot)	NOEL (1 umol/g soil)	Development/Growth	Medium	6824698
88-99-3	75 Day(s), (75 Day(s))	*Lilium davidii* (Lily), Not reported, Not Reported, Laboratory (LILY DEALERS (XIGUOYUAN OF LANZHOU CITY, GANSU PROVINCE, CHINA))	Natural soil, Environmental, Direct application, Not Reported	Unmeasured	0 umol/g soil / 0.01 umol/g soil / 0.05 umol/g soil / 0.25 umol/g soil / 0.5 umol/g soil / 1 umol/g soil	Growth (Growth-Length, Response Site: Root)	NOEL (0.25 umol/g soil); LOEL (0.5 umol/g soil)	Development/Growth	Medium	6824698
88-99-3	75 Day(s), (75 Day(s))	*Lilium davidii* (Lily), Not reported, Not Reported, Laboratory (LILY DEALERS (XIGUOYUAN OF LANZHOU CITY, GANSU PROVINCE, CHINA))	Natural soil, Environmental, Direct application, Not Reported	Unmeasured	0 umol/g soil / 0.01 umol/g soil / 0.05 umol/g soil / 0.25 umol/g soil / 0.5 umol/g soil / 1 umol/g soil	Growth (Growth-Weight, Response Site: Whole organism)	NOEL (0.05 umol/g soil); LOEL (0.25 umol/g soil); NOEL (0.05 umol/g soil); LOEL (0.25 umol/g soil)	Development/Growth	Medium	6824698

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Terrestrial: Vascular plants Extraction Table

CASRN	Exposure and Overall Duration	Test Organism Species, Age, Sex, Source	Exposure Media, Route Grouping, Type, Sample Number	Test Analysis Exposure Parameters	Dose/ Concentration for Each Main Group of the Study	Health Effect as reported by the Study Author(s)	Effect Level as reported by the Study Author(s)*	Health Outcome Identified by the Assessor	Overall Quality Determination	HERO ID
88-99-3	75 Day(s), (75 Day(s))	*Lilium davidii* (Lily), Not reported, Not Reported, Laboratory (LILY DEALERS (XIGUOYUAN OF LANZHOU CITY, GANSU PROVINCE, CHINA))	Natural soil, Environmental, Direct application, Not Reported	Unmeasured	0 umol/g soil / 0.01 umol/g soil / 0.05 umol/g soil / 0.25 umol/g soil / 0.5 umol/g soil / 1 umol/g soil	Biochemical (Enzyme(s)-Peroxidase activity, Response Site: Root)	NR (0.01-1 umol/g soil)	Mechanistic: Oxidative stress (including redox biology); Photosynthesis	Medium	6824698
88-99-3	75 Day(s), (75 Day(s))	*Lilium davidii* (Lily), Not reported, Not Reported, Laboratory (LILY DEALERS (XIGUOYUAN OF LANZHOU CITY, GANSU PROVINCE, CHINA))	Natural soil, Environmental, Direct application, Not Reported	Unmeasured	0 umol/g soil / 0.01 umol/g soil / 0.05 umol/g soil / 0.25 umol/g soil / 0.5 umol/g soil / 1 umol/g soil	Biochemical (Enzyme(s)-Catalase, Response Site: Root)	NOEL (0.25 umol/g soil); LOEL (0.5 umol/g soil)	Mechanistic: Oxidative stress (including redox biology); Photosynthesis	Medium	6824698
88-99-3	75 Day(s), (75 Day(s))	*Lilium davidii* (Lily), Not reported, Not Reported, Laboratory (LILY DEALERS (XIGUOYUAN OF LANZHOU CITY, GANSU PROVINCE, CHINA))	Natural soil, Environmental, Direct application, Not Reported	Unmeasured	0 umol/g soil / 0.01 umol/g soil / 0.05 umol/g soil / 0.25 umol/g soil / 0.5 umol/g soil / 1 umol/g soil	Biochemical (Biochemistry-Malondialdehyde, Response Site: Root)	NOEL (0.5 umol/g soil); LOEL (1 umol/g soil)	Mechanistic: Oxidative stress (including redox biology); Photosynthesis	Medium	6824698
88-99-3	75 Day(s), (75 Day(s))	*Lilium davidii* (Lily), Not reported, Not Reported, Laboratory (LILY DEALERS (XIGUOYUAN OF LANZHOU CITY, GANSU PROVINCE, CHINA))	Natural soil, Environmental, Direct application, Not Reported	Unmeasured	0 umol/g soil / 0.01 umol/g soil / 0.05 umol/g soil / 0.25 umol/g soil / 0.5 umol/g soil / 1 umol/g soil	Biochemical (Biochemistry-Hydrogen peroxide, Response Site: Root)	NOEL (0.25 umol/g soil); LOEL (0.5 umol/g soil)	Mechanistic: Oxidative stress (including redox biology); Photosynthesis	Medium	6824698

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Terrestrial: Vascular plants Extraction Table

CASRN	Exposure and Overall Duration	Test Organism Species, Age, Sex, Source	Exposure Media, Route Grouping, Type, Sample Number	Test Analysis Exposure Parameters	Dose/ Concentration for Each Main Group of the Study	Health Effect as reported by the Study Author(s)	Effect Level as reported by the Study Author(s)*	Health Outcome Identified by the Assessor	Overall Quality Determination	HERO ID
88-99-3	75 Day(s), (75 Day(s))	*Lilium davidii* (Lily), Not reported, Not Reported, Laboratory (LILY DEALERS (XIGUOYUAN OF LANZHOU CITY, GANSU PROVINCE, CHINA))	Natural soil, Environmental, Direct application, Not Reported	Unmeasured	0 umol/g soil / 0.01 umol/g soil / 0.05 umol/g soil / 0.25 umol/g soil / 0.5 umol/g soil / 1 umol/g soil	Biochemical (Biochemistry-Hydroxide content, Response Site: Root)	NOEL (0.25 umol/g soil); LOEL (0.5 umol/g soil)	Mechanistic: Oxidative stress (including redox biology); Photosynthesis	Medium	6824698
88-99-3	75 Day(s), (75 Day(s))	*Lilium davidii* (Lily), Not reported, Not Reported, Laboratory (LILY DEALERS (XIGUOYUAN OF LANZHOU CITY, GANSU PROVINCE, CHINA))	Natural soil, Environmental, Direct application, Not Reported	Unmeasured	0 umol/g soil / 0.01 umol/g soil / 0.05 umol/g soil / 0.25 umol/g soil / 0.5 umol/g soil / 1 umol/g soil	Growth (Growth-Vigor, Response Site: Root)	NOEL (0.5 umol/g soil); LOEL (1 umol/g soil)	Development/Growth	Medium	6824698
88-99-3	75 Day(s), (75 Day(s))	*Lilium davidii* (Lily), Not reported, Not Reported, Laboratory (LILY DEALERS (XIGUOYUAN OF LANZHOU CITY, GANSU PROVINCE, CHINA))	Natural soil, Environmental, Direct application, Not Reported	Unmeasured	0 umol/g soil / 0.01 umol/g soil / 0.05 umol/g soil / 0.25 umol/g soil / 0.5 umol/g soil / 1 umol/g soil	Biochemical (Biochemistry-Chlorophyll A concentration, Response Site: Leaf/needle)	NOEL (0.05 umol/g soil); LOEL (0.25 umol/g soil)	Mechanistic: Oxidative stress (including redox biology); Photosynthesis	Medium	6824698
88-99-3	75 Day(s), (75 Day(s))	*Lilium davidii* (Lily), Not reported, Not Reported, Laboratory (LILY DEALERS (XIGUOYUAN OF LANZHOU CITY, GANSU PROVINCE, CHINA))	Natural soil, Environmental, Direct application, Not Reported	Unmeasured	0 umol/g soil / 0.01 umol/g soil / 0.05 umol/g soil / 0.25 umol/g soil / 0.5 umol/g soil / 1 umol/g soil	Biochemical (Biochemistry-Chlorophyll B concentration, Response Site: Leaf/needle)	NOEL (0.25 umol/g soil); LOEL (0.5 umol/g soil)	Mechanistic: Oxidative stress (including redox biology); Photosynthesis	Medium	6824698

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Terrestrial: Vascular plants Extraction Table

CASRN	Exposure and Overall Duration	Test Organism Species, Age, Sex, Source	Exposure Media, Route Grouping, Type, Sample Number	Test Analysis Exposure Parameters	Dose/ Concentration for Each Main Group of the Study	Health Effect as reported by the Study Author(s)	Effect Level as reported by the Study Author(s)*	Health Outcome Identified by the Assessor	Overall Quality Determination	HERO ID
88-99-3	75 Day(s), (75 Day(s))	*Lilium davidii* (Lily), Not reported, Not Reported, Laboratory (LILY DEALERS (XIGUOYUAN OF LANZHOU CITY, GANSU PROVINCE, CHINA))	Natural soil, Environmental, Direct application, Not Reported	Unmeasured	0 umol/g soil / 0.01 umol/g soil / 0.05 umol/g soil / 0.25 umol/g soil / 0.5 umol/g soil / 1 umol/g soil	Biochemical (Biochemistry-Carotenoid content, Response Site: Leaf/needle)	NOEL (0.05 umol/g soil); LOEL (0.25 umol/g soil)	Mechanistic: Oxidative stress (including redox biology); Photosynthesis	Medium	6824698
88-99-3	75 Day(s), (75 Day(s))	*Lilium davidii* (Lily), Not reported, Not Reported, Laboratory (LILY DEALERS (XIGUOYUAN OF LANZHOU CITY, GANSU PROVINCE, CHINA))	Natural soil, Environmental, Direct application, Not Reported	Unmeasured	0 umol/g soil / 0.01 umol/g soil / 0.05 umol/g soil / 0.25 umol/g soil / 0.5 umol/g soil / 1 umol/g soil	Biochemical (Biochemistry-Phenolic acids, Response Site: Root)	NR (0.01-1 umol/g soil)	Mechanistic: Oxidative stress (including redox biology); Photosynthesis	Medium	6824698
88-99-3	5 Day(s), (15 Day(s))	*Malus prunifolia* (Plumleaf Crab Apple), Seedling, Not Reported, Laboratory (FROM FUPING COUNTY, SHAANXI PROVENCE)	Hydroponic, Environmental, Environmental, unspecified, Not Reported	Unmeasured	0 mM / 1 mM	Biochemical (Enzyme(s)-Peroxidase activity, Response Site: Whole organism)	LOEL (1 mM)	Mechanistic: Oxidative stress (including redox biology); Photosynthesis	High	6813707
88-99-3	5 Day(s), (15 Day(s))	*Malus prunifolia* (Plumleaf Crab Apple), Seedling, Not Reported, Laboratory (FROM FUPING COUNTY, SHAANXI PROVENCE)	Hydroponic, Environmental, Environmental, unspecified, Not Reported	Unmeasured	0 mM / 1 mM	Biochemical (Enzyme(s)-Glutathione reductase, Response Site: Whole organism)	NOEL (1 mM)	Mechanistic: Oxidative stress (including redox biology); Photosynthesis	High	6813707

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Terrestrial: Vascular plants Extraction Table

CASRN	Exposure and Overall Duration	Test Organism Species, Age, Sex, Source	Exposure Media, Route Grouping, Type, Sample Number	Test Analysis Exposure Parameters	Dose/ Concentration for Each Main Group of the Study	Health Effect as reported by the Study Author(s)	Effect Level as reported by the Study Author(s)*	Health Outcome Identified by the Assessor	Overall Quality Determination	HERO ID
88-99-3	5 Day(s), (15 Day(s))	*Malus prunifolia* (Plumleaf Crab Apple), Seedling, Not Reported, Laboratory (FROM FUPING COUNTY, SHAANXI PROVENCE)	Hydroponic, Environmental, Environmental, unspecified, Not Reported	Unmeasured	0 mM / 1 mM	Biochemical (Enzyme(s)-Superoxide dismutase (SOD) enzyme activity, Response Site: Whole organism)	LOEL (1 mM)	Mechanistic: Oxidative stress (including redox biology); Photosynthesis	High	6813707
88-99-3	5 Day(s), (15 Day(s))	*Malus prunifolia* (Plumleaf Crab Apple), Seedling, Not Reported, Laboratory (FROM FUPING COUNTY, SHAANXI PROVENCE)	Hydroponic, Environmental, Environmental, unspecified, Not Reported	Unmeasured	0 mM / 1 mM	Physiology (Physiology-Photosynthesis, Response Site: Not reported)	NOEL (1 mM)	Mechanistic: Oxidative stress (including redox biology); Photosynthesis	High	6813707
88-99-3	5 Day(s), (15 Day(s))	*Malus prunifolia* (Plumleaf Crab Apple), Seedling, Not Reported, Laboratory (FROM FUPING COUNTY, SHAANXI PROVENCE)	Hydroponic, Environmental, Environmental, unspecified, Not Reported	Unmeasured	0 mM / 1 mM	Biochemical (Enzyme(s)-Monodehydroascorbate reductase, Response Site: Whole organism)	NOEL (1 mM)	Mechanistic: Oxidative stress (including redox biology); Photosynthesis	High	6813707
88-99-3	5 Day(s), (15 Day(s))	*Malus prunifolia* (Plumleaf Crab Apple), Seedling, Not Reported, Laboratory (FROM FUPING COUNTY, SHAANXI PROVENCE)	Hydroponic, Environmental, Environmental, unspecified, Not Reported	Unmeasured	0 mM / 1 mM	Biochemical (Enzyme(s)-Ascorbate peroxidase, Response Site: Whole organism)	NOEL (1 mM)	Mechanistic: Oxidative stress (including redox biology); Photosynthesis	High	6813707

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Terrestrial: Vascular plants Extraction Table

CASRN	Exposure and Overall Duration	Test Organism Species, Age, Sex, Source	Exposure Media, Route Grouping, Type, Sample Number	Test Analysis Exposure Parameters	Dose/ Concentration for Each Main Group of the Study	Health Effect as reported by the Study Author(s)	Effect Level as reported by the Study Author(s)*	Health Outcome Identified by the Assessor	Overall Quality Determination	HERO ID
88-99-3	5 Day(s), (15 Day(s))	*Malus prunifolia* (Plumleaf Crab Apple), Seedling, Not Reported, Laboratory (FROM FUPING COUNTY, SHAANXI PROVENCE)	Hydroponic, Environmental, Environmental, unspecified, Not Reported	Unmeasured	0 mM / 1 mM	Biochemical (Enzyme(s)-Catalase, Response Site: Whole organism)	LOEL (1 mM)	Mechanistic: Oxidative stress (including redox biology); Photosynthesis	High	6813707
88-99-3	5 Day(s), (15 Day(s))	*Malus prunifolia* (Plumleaf Crab Apple), Seedling, Not Reported, Laboratory (FROM FUPING COUNTY, SHAANXI PROVENCE)	Hydroponic, Environmental, Environmental, unspecified, Not Reported	Unmeasured	0 mM / 1 mM	Biochemical (Biochemistry-Hydrogen peroxide, Response Site: Whole organism)	NOEL (1 mM)	Mechanistic: Oxidative stress (including redox biology); Photosynthesis	High	6813707
88-99-3	5 Day(s), (15 Day(s))	*Malus prunifolia* (Plumleaf Crab Apple), Seedling, Not Reported, Laboratory (FROM FUPING COUNTY, SHAANXI PROVENCE)	Hydroponic, Environmental, Environmental, unspecified, Not Reported	Unmeasured	0 mM / 1 mM	Biochemical (Enzyme(s)-Dehydroascorbate reductase, Response Site: Whole organism)	NOEL (1 mM)	Mechanistic: Oxidative stress (including redox biology); Photosynthesis	High	6813707
88-99-3	5 Day(s), (15 Day(s))	*Malus prunifolia* (Plumleaf Crab Apple), Seedling, Not Reported, Laboratory (FROM FUPING COUNTY, SHAANXI PROVENCE)	Hydroponic, Environmental, Environmental, unspecified, Not Reported	Unmeasured	0 mM / 1 mM	Biochemical (Biochemistry-Malondialdehyde, Response Site: Whole organism)	LOEL (1 mM)	Mechanistic: Oxidative stress (including redox biology); Photosynthesis	High	6813707

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Terrestrial: Vascular plants Extraction Table

CASRN	Exposure and Overall Duration	Test Organism Species, Age, Sex, Source	Exposure Media, Route Grouping, Type, Sample Number	Test Analysis Exposure Parameters	Dose/ Concentration for Each Main Group of the Study	Health Effect as reported by the Study Author(s)	Effect Level as reported by the Study Author(s)*	Health Outcome Identified by the Assessor	Overall Quality Determination	HERO ID
88-99-3	10 Day(s), (15 Day(s))	*Malus prunifolia* (Plumleaf Crab Apple), Seedling, Not Reported, Laboratory (FROM FUPING COUNTY, SHAANXI PROVENCE)	Hydroponic, Environmental, Environmental, unspecified, Not Reported	Unmeasured	0 mM / 1 mM	Biochemical (Enzyme(s)-Glutathione reductase, Response Site: Whole organism)	LOEL (1 mM)	Mechanistic: Oxidative stress (including redox biology); Photosynthesis	High	6813707
88-99-3	10 Day(s), (15 Day(s))	*Malus prunifolia* (Plumleaf Crab Apple), Seedling, Not Reported, Laboratory (FROM FUPING COUNTY, SHAANXI PROVENCE)	Hydroponic, Environmental, Environmental, unspecified, Not Reported	Unmeasured	0 mM / 1 mM	Biochemical (Enzyme(s)-Superoxide dismutase (SOD) enzyme activity, Response Site: Whole organism)	LOEL (1 mM)	Mechanistic: Oxidative stress (including redox biology); Photosynthesis	High	6813707
88-99-3	10 Day(s), (15 Day(s))	*Malus prunifolia* (Plumleaf Crab Apple), Seedling, Not Reported, Laboratory (FROM FUPING COUNTY, SHAANXI PROVENCE)	Hydroponic, Environmental, Environmental, unspecified, Not Reported	Unmeasured	0 mM / 1 mM	Physiology (Physiology-Photosynthesis, Response Site: Not reported)	LOEL (1 mM)	Mechanistic: Oxidative stress (including redox biology); Photosynthesis	High	6813707
88-99-3	10 Day(s), (15 Day(s))	*Malus prunifolia* (Plumleaf Crab Apple), Seedling, Not Reported, Laboratory (FROM FUPING COUNTY, SHAANXI PROVENCE)	Hydroponic, Environmental, Environmental, unspecified, Not Reported	Unmeasured	0 mM / 1 mM	Biochemical (Biochemistry-Hydrogen peroxide, Response Site: Whole organism)	LOEL (1 mM)	Mechanistic: Oxidative stress (including redox biology); Photosynthesis	High	6813707

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Terrestrial: Vascular plants Extraction Table

CASRN	Exposure and Overall Duration	Test Organism Species, Age, Sex, Source	Exposure Media, Route Grouping, Type, Sample Number	Test Analysis Exposure Parameters	Dose/ Concentration for Each Main Group of the Study	Health Effect as reported by the Study Author(s)	Effect Level as reported by the Study Author(s)*	Health Outcome Identified by the Assessor	Overall Quality Determination	HERO ID
88-99-3	10 Day(s), (15 Day(s))	*Malus prunifolia* (Plumleaf Crab Apple), Seedling, Not Reported, Laboratory (FROM FUPING COUNTY, SHAANXI PROVENCE)	Hydroponic, Environmental, Environmental, unspecified, Not Reported	Unmeasured	0 mM / 1 mM	Biochemical (Enzyme(s)-Catalase, Response Site: Whole organism)	LOEL (1 mM)	Mechanistic: Oxidative stress (including redox biology); Photosynthesis	High	6813707
88-99-3	10 Day(s), (15 Day(s))	*Malus prunifolia* (Plumleaf Crab Apple), Seedling, Not Reported, Laboratory (FROM FUPING COUNTY, SHAANXI PROVENCE)	Hydroponic, Environmental, Environmental, unspecified, Not Reported	Unmeasured	0 mM / 1 mM	Biochemical (Enzyme(s)-Ascorbate peroxidase, Response Site: Whole organism)	LOEL (1 mM)	Mechanistic: Oxidative stress (including redox biology); Photosynthesis	High	6813707
88-99-3	10 Day(s), (15 Day(s))	*Malus prunifolia* (Plumleaf Crab Apple), Seedling, Not Reported, Laboratory (FROM FUPING COUNTY, SHAANXI PROVENCE)	Hydroponic, Environmental, Environmental, unspecified, Not Reported	Unmeasured	0 mM / 1 mM	Biochemical (Enzyme(s)-Dehydroascorbate reductase, Response Site: Whole organism)	LOEL (1 mM)	Mechanistic: Oxidative stress (including redox biology); Photosynthesis	High	6813707
88-99-3	10 Day(s), (15 Day(s))	*Malus prunifolia* (Plumleaf Crab Apple), Seedling, Not Reported, Laboratory (FROM FUPING COUNTY, SHAANXI PROVENCE)	Hydroponic, Environmental, Environmental, unspecified, Not Reported	Unmeasured	0 mM / 1 mM	Biochemical (Enzyme(s)-Peroxidase activity, Response Site: Whole organism)	LOEL (1 mM)	Mechanistic: Oxidative stress (including redox biology); Photosynthesis	High	6813707

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Terrestrial: Vascular plants Extraction Table

CASRN	Exposure and Overall Duration	Test Organism Species, Age, Sex, Source	Exposure Media, Route Grouping, Type, Sample Number	Test Analysis Exposure Parameters	Dose/ Concentration for Each Main Group of the Study	Health Effect as reported by the Study Author(s)	Effect Level as reported by the Study Author(s)*	Health Outcome Identified by the Assessor	Overall Quality Determination	HERO ID
88-99-3	10 Day(s), (15 Day(s))	*Malus prunifolia* (Plumleaf Crab Apple), Seedling, Not Reported, Laboratory (FROM FUPING COUNTY, SHAANXI PROVENCE)	Hydroponic, Environmental, Environmental, unspecified, Not Reported	Unmeasured	0 mM / 1 mM	Biochemical (Biochemistry-Malondialdehyde, Response Site: Whole organism)	LOEL (1 mM)	Mechanistic: Oxidative stress (including redox biology); Photosynthesis	High	6813707
88-99-3	10 Day(s), (15 Day(s))	*Malus prunifolia* (Plumleaf Crab Apple), Seedling, Not Reported, Laboratory (FROM FUPING COUNTY, SHAANXI PROVENCE)	Hydroponic, Environmental, Environmental, unspecified, Not Reported	Unmeasured	0 mM / 1 mM	Biochemical (Enzyme(s)-Monodehydroascorbate reductase, Response Site: Whole organism)	LOEL (1 mM)	Mechanistic: Oxidative stress (including redox biology); Photosynthesis	High	6813707
88-99-3	15 Day(s), (15 Day(s))	*Malus prunifolia* (Plumleaf Crab Apple), Seedling, Not Reported, Laboratory (FROM FUPING COUNTY, SHAANXI PROVENCE)	Hydroponic, Environmental, Environmental, unspecified, Not Reported	Unmeasured	0 mM / 1 mM	Biochemical (Enzyme(s)-Peroxidase activity, Response Site: Whole organism)	LOEL (1 mM)	Mechanistic: Oxidative stress (including redox biology); Photosynthesis	High	6813707
88-99-3	15 Day(s), (15 Day(s))	*Malus prunifolia* (Plumleaf Crab Apple), Seedling, Not Reported, Laboratory (FROM FUPING COUNTY, SHAANXI PROVENCE)	Hydroponic, Environmental, Environmental, unspecified, Not Reported	Unmeasured	0 mM / 1 mM	Growth (Growth-Length, Response Site: Root)	LOEL (1 mM)	Development/Growth	High	6813707

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Terrestrial: Vascular plants Extraction Table

CASRN	Exposure and Overall Duration	Test Organism Species, Age, Sex, Source	Exposure Media, Route Grouping, Type, Sample Number	Test Analysis Exposure Parameters	Dose/ Concentration for Each Main Group of the Study	Health Effect as reported by the Study Author(s)	Effect Level as reported by the Study Author(s)*	Health Outcome Identified by the Assessor	Overall Quality Determination	HERO ID
88-99-3	15 Day(s), (15 Day(s))	*Malus prunifolia* (Plumleaf Crab Apple), Seedling, Not Reported, Laboratory (FROM FUPING COUNTY, SHAANXI PROVENCE)	Hydroponic, Environmental, Environmental, unspecified, Not Reported	Unmeasured	0 mM / 1 mM	Growth (Growth-Weight, Response Site: Whole organism)	LOEL (1 mM); LOEL (1 mM)	Development/Growth	High	6813707
88-99-3	15 Day(s), (15 Day(s))	*Malus prunifolia* (Plumleaf Crab Apple), Seedling, Not Reported, Laboratory (FROM FUPING COUNTY, SHAANXI PROVENCE)	Hydroponic, Environmental, Environmental, unspecified, Not Reported	Unmeasured	0 mM / 1 mM	Biochemical (Biochemistry-Malondialdehyde, Response Site: Whole organism)	LOEL (1 mM)	Mechanistic: Oxidative stress (including redox biology); Photosynthesis	High	6813707
88-99-3	15 Day(s), (15 Day(s))	*Malus prunifolia* (Plumleaf Crab Apple), Seedling, Not Reported, Laboratory (FROM FUPING COUNTY, SHAANXI PROVENCE)	Hydroponic, Environmental, Environmental, unspecified, Not Reported	Unmeasured	0 mM / 1 mM	Growth (Growth-Length, Response Site: Shoot)	LOEL (1 mM)	Development/Growth	High	6813707
88-99-3	15 Day(s), (15 Day(s))	*Malus prunifolia* (Plumleaf Crab Apple), Seedling, Not Reported, Laboratory (FROM FUPING COUNTY, SHAANXI PROVENCE)	Hydroponic, Environmental, Environmental, unspecified, Not Reported	Unmeasured	0 mM / 1 mM	Biochemical (Enzyme(s)-Ascorbate peroxidase, Response Site: Whole organism)	LOEL (1 mM)	Mechanistic: Oxidative stress (including redox biology); Photosynthesis	High	6813707

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Terrestrial: Vascular plants Extraction Table

CASRN	Exposure and Overall Duration	Test Organism Species, Age, Sex, Source	Exposure Media, Route Grouping, Type, Sample Number	Test Analysis Exposure Parameters	Dose/ Concentration for Each Main Group of the Study	Health Effect as reported by the Study Author(s)	Effect Level as reported by the Study Author(s)*	Health Outcome Identified by the Assessor	Overall Quality Determination	HERO ID
88-99-3	15 Day(s), (15 Day(s))	*Malus prunifolia* (Plumleaf Crab Apple), Seedling, Not Reported, Laboratory (FROM FUPING COUNTY, SHAANXI PROVENCE)	Hydroponic, Environmental, Environmental, unspecified, Not Reported	Unmeasured	0 mM / 1 mM	Biochemical (Enzyme(s)-Monodehydroascorbate reductase, Response Site: Whole organism)	LOEL (1 mM)	Mechanistic: Oxidative stress (including redox biology); Photosynthesis	High	6813707
88-99-3	15 Day(s), (15 Day(s))	*Malus prunifolia* (Plumleaf Crab Apple), Seedling, Not Reported, Laboratory (FROM FUPING COUNTY, SHAANXI PROVENCE)	Hydroponic, Environmental, Environmental, unspecified, Not Reported	Unmeasured	0 mM / 1 mM	Physiology (Physiology-Photosynthesis, Response Site: Not reported)	LOEL (1 mM)	Mechanistic: Oxidative stress (including redox biology); Photosynthesis	High	6813707
88-99-3	15 Day(s), (15 Day(s))	*Malus prunifolia* (Plumleaf Crab Apple), Seedling, Not Reported, Laboratory (FROM FUPING COUNTY, SHAANXI PROVENCE)	Hydroponic, Environmental, Environmental, unspecified, Not Reported	Unmeasured	0 mM / 1 mM	Biochemical (Enzyme(s)-Superoxide dismutase (SOD) enzyme activity, Response Site: Whole organism)	LOEL (1 mM)	Mechanistic: Oxidative stress (including redox biology); Photosynthesis	High	6813707
88-99-3	15 Day(s), (15 Day(s))	*Malus prunifolia* (Plumleaf Crab Apple), Seedling, Not Reported, Laboratory (FROM FUPING COUNTY, SHAANXI PROVENCE)	Hydroponic, Environmental, Environmental, unspecified, Not Reported	Unmeasured	0 mM / 1 mM	Biochemical (Enzyme(s)-Dehydroascorbate reductase, Response Site: Whole organism)	LOEL (1 mM)	Mechanistic: Oxidative stress (including redox biology); Photosynthesis	High	6813707

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Terrestrial: Vascular plants Extraction Table

CASRN	Exposure and Overall Duration	Test Organism Species, Age, Sex, Source	Exposure Media, Route Grouping, Type, Sample Number	Test Analysis Exposure Parameters	Dose/ Concentration for Each Main Group of the Study	Health Effect as reported by the Study Author(s)	Effect Level as reported by the Study Author(s)*	Health Outcome Identified by the Assessor	Overall Quality Determination	HERO ID
88-99-3	15 Day(s), (15 Day(s))	*Malus prunifolia* (Plumleaf Crab Apple), Seedling, Not Reported, Laboratory (FROM FUPING COUNTY, SHAANXI PROVENCE)	Hydroponic, Environmental, Environmental, unspecified, Not Reported	Unmeasured	0 mM / 1 mM	Biochemical (Enzyme(s)-Glutathione reductase, Response Site: Whole organism)	LOEL (1 mM)	Mechanistic: Oxidative stress (including redox biology); Photosynthesis	High	6813707
88-99-3	15 Day(s), (15 Day(s))	*Malus prunifolia* (Plumleaf Crab Apple), Seedling, Not Reported, Laboratory (FROM FUPING COUNTY, SHAANXI PROVENCE)	Hydroponic, Environmental, Environmental, unspecified, Not Reported	Unmeasured	0 mM / 1 mM	Biochemical (Biochemistry-Hydrogen peroxide, Response Site: Whole organism)	LOEL (1 mM)	Mechanistic: Oxidative stress (including redox biology); Photosynthesis	High	6813707
88-99-3	15 Day(s), (15 Day(s))	*Malus prunifolia* (Plumleaf Crab Apple), Seedling, Not Reported, Laboratory (FROM FUPING COUNTY, SHAANXI PROVENCE)	Hydroponic, Environmental, Environmental, unspecified, Not Reported	Unmeasured	0 mM / 1 mM	Biochemical (Enzyme(s)-Catalase, Response Site: Whole organism)	LOEL (1 mM)	Mechanistic: Oxidative stress (including redox biology); Photosynthesis	High	6813707
88-99-3	7 Day(s), (7 Day(s))	*Nicotiana sp.* (Tobacco), Seed, Not Reported, Laboratory	Filter paper, Environmental, Environmental, unspecified, 50 Organism	Unmeasured	0 g/L / 0.1 g/L / 0.25 g/L / 0.5 g/L	Reproduction (Reproduction-Germination, Response Site: Not reported)	NR (0.1-0.5 g/L)	Reproductive/Teratogenic	Uninformative	6968271
88-99-3	7 Day(s), (7 Day(s))	*Nicotiana sp.* (Tobacco), Seed, Not Reported, Laboratory	Filter paper, Environmental, Environmental, unspecified, 20 Organism	Unmeasured	0 g/L / 0.1 g/L / 0.25 g/L / 0.5 g/L	Growth (Growth-Length,Weight, Response Site: Root)	NR (0.1-0.5 g/L)	Development/Growth	Uninformative	6968271

* If multiple extractions contained all identical information except the effect level, extraction rows were collapsed and the differing levels are listed by comma in this row.

Terrestrial: Fungi Extraction Table

CASRN	Exposure and Overall Duration	Test Organism Species, Age, Sex, Source	Exposure Media, Route Grouping, Type, Sample Number	Test Analysis Exposure Parameters	Dose/ Concentration for Each Main Group of the Study	Health Effect as reported by the Study Author(s)	Effect Level as reported by the Study Author(s)*	Health Outcome Identified by the Assessor	Overall Quality Determination	HERO ID
88-99-3	24 Hour(s), (316 Hour(s))	*Sclerotinia sclerotiorum* (Fungus), Not reported, Not Reported, Laboratory (ISOLATED FROM GREENHOUSE GROWN EGGPLANT)	Culture, Environmental, Culture medium, Not Reported	Unmeasured	0 mg/L / 100 mg/L	Population (Population-Abundance, Response Site: Not reported)	NOEL (100 mg/L)	Development/Growth	Medium	6826077
88-99-3	32 Hour(s), (316 Hour(s))	*Sclerotinia sclerotiorum* (Fungus), Not reported, Not Reported, Laboratory (ISOLATED FROM GREENHOUSE GROWN EGGPLANT)	Culture, Environmental, Culture medium, Not Reported	Unmeasured	0 mg/L / 100 mg/L	Population (Population-Abundance, Response Site: Not reported)	NOEL (100 mg/L)	Development/Growth	Medium	6826077
88-99-3	48 Hour(s), (316 Hour(s))	*Sclerotinia sclerotiorum* (Fungus), Not reported, Not Reported, Laboratory (ISOLATED FROM GREENHOUSE GROWN EGGPLANT)	Culture, Environmental, Culture medium, Not Reported	Unmeasured	0 mg/L / 100 mg/L	Population (Population-Abundance, Response Site: Not reported)	NOEL (100 mg/L)	Development/Growth	Medium	6826077
88-99-3	56 Hour(s), (316 Hour(s))	*Sclerotinia sclerotiorum* (Fungus), Not reported, Not Reported, Laboratory (ISOLATED FROM GREENHOUSE GROWN EGGPLANT)	Culture, Environmental, Culture medium, Not Reported	Unmeasured	0 mg/L / 100 mg/L	Population (Population-Abundance, Response Site: Not reported)	NOEL (100 mg/L)	Development/Growth	Medium	6826077
88-99-3	72 Hour(s), (316 Hour(s))	*Sclerotinia sclerotiorum* (Fungus), Not reported, Not Reported, Laboratory (ISOLATED FROM GREENHOUSE GROWN EGGPLANT)	Culture, Environmental, Culture medium, Not Reported	Unmeasured	0 mg/L / 100 mg/L	Population (Population-Abundance, Response Site: Not reported)	LOEL (100 mg/L)	Development/Growth	Medium	6826077

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Terrestrial: Fungi Extraction Table

CASRN	Exposure and Overall Duration	Test Organism Species, Age, Sex, Source	Exposure Media, Route Grouping, Type, Sample Number	Test Analysis Exposure Parameters	Dose/ Concentration for Each Main Group of the Study	Health Effect as reported by the Study Author(s)	Effect Level as reported by the Study Author(s)*	Health Outcome Identified by the Assessor	Overall Quality Determination	HERO ID
88-99-3	80 Hour(s), (316 Hour(s))	*Sclerotinia sclerotiorum* (Fungus), Not reported, Not Reported, Laboratory (ISOLATED FROM GREENHOUSE GROWN EGGPLANT)	Culture, Environmental, Culture medium, Not Reported	Unmeasured	0 mg/L / 100 mg/L	Population (Population-Abundance, Response Site: Not reported)	LOEL (100 mg/L)	Development/Growth	Medium	6826077
88-99-3	120-320 Hour(s), (316 Hour(s))	*Sclerotinia sclerotiorum* (Fungus), Not reported, Not Reported, Laboratory (ISOLATED FROM GREENHOUSE GROWN EGGPLANT)	Culture, Environmental, Culture medium, Not Reported	Unmeasured	0 mg/L / 100 mg/L	Population (Population-Abundance, Response Site: Not reported)	NR (100 mg/L)	Development/Growth	Medium	6826077

* If multiple extractions contained all identical information except the effect level, extraction rows were collapsed and the differing levels are listed by comma in this row.

Data Extraction of Rodent Data for the Application of Environmental Hazard

CASRN	Exposure and Overall Duration	Test Organism Species, Age, Sex, Strain	Exposure Type	Test Analysis Exposure Parameters	Dose/ Concentration for Each Main Group of the Study	Hazard Effect/ Hazard Level	Effect Level as reported by the Study Author(s)	Health Outcome Identified by the Assessor	Overall Quality Determination	HERO ID
85-44-9	9d, (21 to 23d)	Rat (Rattus norvegicus), Sampling Age: Adult Exposure Age: Adult, Female, Pregnant Wistar Rats	Dietary	Dietary	1.25, 2.5, or 5.0% PA	1021 mg/kg-bw/d	NOAEL	Decrease in maternal weight gain and food consumption	High	790543
85-44-9	1 d, (14d)	Rat (Rattus norvegicus), Sampling Age: Adult Exposure Age: Adult, Male, Sprague-Dawley rats	Oral gavage	Nominal	250 mg/kg/day	250 mg/kg-bw/d	LOAEL	Growth	High	792143
85-44-9	1 d, (28d)	Rat (Rattus norvegicus), Sampling Age: Adult Exposure Age: Adult, Male, Spargue-Dawley rats	Oral gavage	Nominal	250 mg/kg bw/d	250 mg/kg-bw/d	LOAEL	Growth	High	697382
85-44-9	7d, (7d)	Rat (Rattus norvegicus), Sampling Age: Adult Exposure Age: Adult, Male, Wistar Rats	Oral	Nominal	850 mg/kg/day	850 mg/kg-bw/d	NOAEL	nan	Medium	699519
85-44-9	36d, (36d)	Rat (Rattus norvegicus), Sampling Age: Adult Exposure Age: Adult, Male, Wistar Rats	Dietary	Dietary	0.5 and 5%	5000 mg/kg-bw/d	NOAEL	nan	Medium	61568

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Data Extraction of Rodent Data for the Application of Environmental Hazard

CASRN	Exposure and Overall Duration	Test Organism Species, Age, Sex, Strain	Exposure Type	Test Analysis Exposure Parameters	Dose/ Concentration for Each Main Group of the Study	Hazard Effect/ Hazard Level	Effect Level as reported by the Study Author(s)	Health Outcome Identified by the Assessor	Overall Quality Determination	HERO ID
85-44-9	32 or 72 wk, (105 wk)	Rat (Rattus norvegicus), Sampling Age: Adult Exposure Age: Adult, Male and Female, F344 Rats	Dietary	Dietary	7500 and 15000, or 12500 and 25000 (m) or 6250 or 12500 (f) ppm	2500 mg/kg-bw/d	NOAEL	Decrease (24-26%) in body weight (both sexes)	Uninformative	63768
85-44-9	32 or 72 wk, (105 wk)	Mouse (Mus musculus), Sampling Age: Adult Exposure Age: Adult, Male and Female, B6C3F1	Dietary	Dietary	7500 and 15000, or 12500 and 25000 (m) or 6250 or 12500 (f) ppm	7500 mg/kg-bw/d	NOAEL	nan	Uninformative	63768
85-44-9	32 or 72 wk, (105 wk)	Rat (Rattus norvegicus), Sampling Age: Adult Exposure Age: Adult, Male and Female, F344 Rats	Dietary	Dietary	7500 and 15000, or 12500 and 25000 (m) or 6250 or 12500 (f) ppm	375 mg/kg-bw/d	NOAEL	Decrease male body weight	Uninformative	63768
85-44-9	32 or 72 wk, (105 wk)	Mouse (Mus musculus), Sampling Age: Adult Exposure Age: Adult, Male and Female, B6C3F1	Dietary	Dietary	7500 and 15000, or 12500 and 25000 (m) or 6250 or 12500 (f) ppm	1803 mg/kg-bw/d	LOAEL	Decrease terminal body weight, increased incidence of histopathology in lung	Uninformative	63768
85-44-9	1wk, (1wk)	Rat (Rattus norvegicus), Sampling Age: Adult Exposure Age: Adult, Male, Wistar Rats	Dietary	Dietary	2% PA	2000 mg/kg-bw/d	NOAEL	nan	Not Determined	61572
85-44-9	9d, (21 to 23d)	Rat (Rattus norvegicus), Sampling Age: Adult Exposure Age: Adult, Male and Female, Wistar Rats	Dietary	Dietary	2.5 and 5% PA	1763 mg/kg-bw/d	LOAEL	Decrease in F1 offspring body weight on PND 90, cardiovascular effects	Medium	3071054

Phthalic anhydride - Acute (less than or equal to 24 hr)

Guideline and Animal Species, Strain, Sex	Exposure Route and Exposure Duration	Study-wide POD and Dose/ Concentration(s)	Summary	Major Limitations	Principal Target Organs/Systems and OQD*	Citation and HERO ID
Adherence to a guideline was not specified. Rat; Wistar - [rat]; Male	Oral: Gavage Single dose Single dose	**POD: 1530 mg/kg (LD50, mortality)** 0.1, 0.5, 1, 2, 3.1, 5g/kg	In an acute oral toxicity study, male Wister II rats (10/group) were exposed by gavage to a single phthalic anhydride dose (purity not reported) of 0.1, 0.5, 1, 2, 3.1, or 5 g/kg and then observed for mortality and clinical signs of toxicity for 14 days. No animals died in the 0.1 g/kg group. Mortality increased with increasing dose in groups exposed to $\geq$ 0.5 g/kg, with 100% mortality at 5 g/kg. Test animals that succumbed to exposure died within 4 days of dosing. Clinical signs (sedation and disturbance of equilibrium) were observed in all test animals exposed to $\geq$ 0.5 g/kg. An author-reported LD50 of 1.53 g/kg (1530 mg/kg) was reported for phthalic anhydride.	Insufficient details were reported on animal husbandry conditions and test material delivery (e.g. gavage volume).	Mortality, Clinical signs: Medium	Bayer AG 1978 5353568
No guidelines cited Rabbit; New Zealand White - [rabbit]; Both	Dermal 4 hours The patch was removed after 4 hrs.	**POD: Neat: very mild irritant; Moistened: moderate irritant** 0.5grams	See footnotes for full summary [1]	Unmoistened test substance was applied to one site on the rabbit and 7 days later moistened test substance was applied to another area on the same rabbit. There is uncertainty if the response following the second application may involve a sensitization response.	Irritation: High	Exxon Biomedical, 1988 12980183
Study did not follow guideline or GLP practices Guinea pig; Dunkin-Hartley - [guinea pig]; Both	Intradermal injection (sensitization); inhalation (dust; challenge) 1 days Animals were administered single intradermal injections (sensitization) on Day 1 (100ul of 0, 0.03, 0.1 and 0.3% phthalic anhydride in corn oil). At challenge, animals were exposed to phthalic anhydride dust (11-29 mg/m3 (exp. 1) in an argon atmosphere or 9-48 mg/m3 (exp. 2) in dry-air, nose only, for 15 minutes).	**POD: Phthalic anhydride is a respiratory sensitizer in guinea pigs intradermally sensitized to phthalic acid and challenged via inhalation.** 0, 0.03, 0.1, 0.3%	See footnotes for full summary [2]	This was an animal model validation study using known respiratory sensitizers including PHA. Analytical validation of exposure concentrations was either not performed, or not reported. MMAD and GSD values were not provided.	Sensitization: Uninformative	Blaikie et al. 1994 5177461

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Phthalic anhydride - Acute (less than or equal to 24 hr)

Guideline and Animal Species, Strain, Sex	Exposure Route and Exposure Duration	Study-wide POD and Dose/ Concentration(s)	Summary	Major Limitations	Principal Target Organs/Systems and OQD*	Citation and HERO ID
Study did not follow guideline or GLP practices Guinea pig; Dunkin-Hartley - [guinea pig]; Both	Intradermal injection (sensitization); inhalation (dust; challenge) 1 days Animals were administered a single intradermal injection (sensitization) on Day 1 (100ul of 0.3% phthalic anhydride in 6% acetone in corn oil). At challenge, animals were exposed to phthalic anhydride dust (52 mg/m3, for experiment 2 - see below), nose only, for 15 minutes.	**POD: Positive for sensitization in guinea pigs dermally sensitized and challenged via inhalation.** 0, 0.3%	See footnotes for full summary [3]	This was an animal model validation study using known respiratory sensitizers including PHA. It was determined by the study authors that the physicochemical characteristics of the PHA used for the inhalation challenge (i.e., the rapid oxidation of particulate PHA) may have influenced the induction of a pulmonary response and that the protocol should be modified to freshly grinding PHA just prior to use and creating test atmosphere with very dry air or argon (an inert gas). Even after modification of the protocol, the study authors indicated a need for extensive preliminary experimentation to optimise the inhalation challenge conditions. Analytical verification of the exposure concentrations was either not performed, or not reported. MMAD and GSD values were not provided.	Sensitization: Uninformative	Blaikie et al. 1994 5177461
No guideline followed Mouse; CD-1 - [mouse]; Female	ip injection CD-1 dams were administered 3 ip doses of phthalic anhydride on GDs 8-10. Authors state that 4 or more dose levels were utilized for the majority of chemicals (8 chemicals were tested in this study); however, the precise doses of administered phthalic anhydride were not reported.	**POD: Not applicable. This study does not allow for the identification of a POD because the utilized dose groups were not reported.** 0mmol/kg/day	CD-1 dams were administered 3 daily ip injections of phthalic anhydride (dose levels not reported) on GDs 8-10. Dams were then sacrificed on GD 18, uteri were removed, and contents were examined for the numbers of live, dead and resorbed fetuses. Fetuses were examined for gross malformations, fetal weight, visceral defects and head and skeletal anomalies. Fetal malformations were reported as a relative teratogenic index. The observed incidence of various malformations and variations were not reported.	Exposure levels not reported; incidence of various malformations not reported	Reproductive/Developmental: Uninformative	Fabro et al. 1982 63760

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Phthalic anhydride - Acute (less than or equal to 24 hr)

Guideline and Animal Species, Strain, Sex	Exposure Route and Exposure Duration	Study-wide POD and Dose/ Concentration(s)	Summary	Major Limitations	Principal Target Organs/Systems and OQD*	Citation and HERO ID
Adherence to a test guideline was not specified. Study complied with GLP. Rat; Sprague-Dawley - [rat]; Male	Inhalation: Particulate 0.165 hours Exposed for at least 10 minutes; exposure to phthalic acid (0.93% of total collected sample) and phthalic anhydride vapor (0.05% of sample) also occurred.	**POD: 486 mg/m3 (NOAEL, respiratory rate)(0.486 mg/L)** 0.486 mg chemical / L air	Four male Sprague-Dawley (Crl:CDBR) rats were exposed to phthalic anhydride (purity 99.9%) dust via head-only inhalation chambers at a maximum obtainable chamber concentration measured at 0.486 mg/L (nominal concentration 42 mg/L, gravimetric concentration 0.574 mg/L) for a minimum of 10 minutes. At the time of exposure, animals weighed between 290-305 g. Respiratory rates were measured for each animal using a ventilated plexiglass plethysmograph. Animals were acclimated to the plethysmographs for 0.5-1 hour on the day prior to exposure. On the day of exposure, respiratory rates were calculated for 20-second intervals prior to the exposure, during the exposure, and after the exposure. The respiratory rates prior to exposure for each animal served as the control data. The average respiratory rates pre-exposure, during, and post-exposure were 132.1, 128.8, and 130.0 breaths/minute, with respective percentages of the pre-exposure mean at 100%, 97.5%, and 98.4%. The test substance was considered to not have an effect on respiratory rate.	No other endpoints were evaluated. Exposure to phthalic acid (0.93% of total collected sample) and phthalic anhydride vapor (0.05% of sample) also occurred; the mean phthalic acid concentration was measured at 0.00483 mg/L. The exact timing of the respiratory rate measurements was not provided.	Lung/Respiratory: High	IIT Research Institute, 1995 6301186
Adherence to a test guideline was not specified. Study complied with GLP. Rat; Sprague-Dawley - [rat]; Male	Inhalation: Vapor 0.165 hours Exposed for at least 10 minutes	**POD: 11 mg/m3 (NOAEL, respiratory rate)(0.011 mg/L)** 0.011 mg chemical / L air	Four male Sprague-Dawley (Crl:CDBR) rats were exposed to phthalic anhydride (purity 99.9%) vapor via head-only inhalation chambers at a maximum obtainable chamber concentration measured at 0.011 mg/L (nominal concentration 0.03 mg/L) for a minimum of 10 minutes. At the time of exposure, animals weighed between 210-243 g. Respiratory rates were measured for each animal using a ventilated plexiglass plethysmograph. Animals were acclimated to the plethysmographs for 0.5-1 hour on the day prior to exposure. On the day of exposure, respiratory rates were calculated for 10-second intervals prior to the exposure, during the exposure, and after the exposure. The respiratory rates prior to exposure for each animal served as the control data. The baseline measurement prior to exposure for one animal was not stable and therefore the study authors excluded this animal in the final calculations. The average respiratory rates pre-exposure, during, and post-exposure were 118.9, 116.0, and 119.8 breaths/minute, with respective percentages of the pre-exposure mean at 100%, 97.6% and 100.8%. The test substance was considered to not have an effect on respiratory rate.	No information was provided for the respiratory rates of the animal that was excluded. Only 3 rats were included in the final analysis. No other endpoints were evaluated. The exact timing of the respiratory rate measurements was not provided.	Lung/Respiratory: High	IIT Research Institute, 1995 6301188

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Phthalic anhydride - Acute (less than or equal to 24 hr)

Guideline and Animal Species, Strain, Sex	Exposure Route and Exposure Duration	Study-wide POD and Dose/ Concentration(s)	Summary	Major Limitations	Principal Target Organs/Systems and OQD*	Citation and HERO ID
Adherence to a guideline was not specified. Rabbit; New Zealand White - [rabbit]; Both	Eye instillation 1 days Single application, dose not reported.	**POD: Uninformative – not suitable for POD determination** 0Dose groups and units not provided	In an acute eye irritation toxicity study, male and female New Zealand White rabbits (2/group) were exposed to phthalic anhydride (purity not reported) by instillation into the conjunctival sac of the eye and then observed for irritation for 7 days. Volume or concentration of the test chemical administered was not reported.The authors report that the cornea was partially, temporarily opaque. No additional details were provided. The authors classified phthalic anhydride as “moderately irritant”.	No dose/concentration information was reported. The study provides no information on outcome assessment methodology and does not report irritation scores.	Irritation: Low	Bayer IT 1979 12980172
Adherence to a guideline was not specified. Rabbit; New Zealand White - [rabbit]; Both	Dermal 1 days Single dose	**POD: 500 mg/animal (Negative, skin irritation)** 500mg	In an acute dermal toxicity study, male and female New Zealand White rabbits (2 animals/group) were dermally exposed to phthalic anhydride (purity not reported); 500 mg/animal was applied to the ear (the ”inner surface of the spoon”) of each animal. The ear was covered with plaster bandages, which were removed after 24 hours, and the test area was washed with soap, water, and vegetable oil. The test animals were observed for irritation for 7 days.The authors classified phthalic anhydride as a “non-irritant”.	This study has significant reporting limitations. The study provides no information on outcome assessment methodology and does not report irritation scores. It is unclear what method was used to assess the outcome of interest.	Irritation: Low	Bayer IT 1979 12980172
No guideline stated. Mouse; Swiss albino; Male	intraperitoneal 1 days	**POD: 50 mg/kg/day (NOAEL, sperm head abnormality)** 0, 50, 100, 150, 200, 300mg/kg	In a sperm head abnormality study, male Swiss albino mice (5/group/timepoint) were administered a single i.p injection of 0, 50, 100, 150, 200 or 300 mg/kg/day phthalic acid in 10% DMSO diluted in phosphate buffered saline one time. Mice were sacrificed 1, 3 or 5 weeks after treatment and smears of spermatozoa from the epididymis were made. 2,500 sperm heads/dose from 5 mice were scored as either having normal or abnormal morphology. One week after treatment, the number of abnormal sperm heads significantly increased at 100 (2-fold), 150 (2.6-fold), 200 (3.2-fold) and 300 mg/kg/day (3.5-fold) compared to control. Three weeks after treatment there was a significant increase in abnormal sperm heads in the 100 (2.2-fold), 150 (3.0-fold) and 200mg/kg/day (3.3-fold) groups. The 4.4-fold increase at 300 mg/kg/day three weeks after treatment was not statistically significant. Five weeks after treatment only the 300 mg/kg/day group had significantly increased number of abnormal sperm (2.5-fold). The most common types of abnormal sperm seen were amorphous, elongated, without a hook and giant amorphous.	Effects on food consumption, body weight gain, clinical signs not evaluated. Route of administration (i.p. injection) lacks human relevance	Reproductive/Developmental: High	Jha et al. 1998 1336719

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Phthalic anhydride - Acute (less than or equal to 24 hr)

Guideline and Animal Species, Strain, Sex	Exposure Route and Exposure Duration	Study-wide POD and Dose/ Concentration(s)	Summary	Major Limitations	Principal Target Organs/Systems and OQD*	Citation and HERO ID
No guideline stated. Mouse; Swiss albino; Male	intraperitoneal 1 days	**POD: 400 mg/kg/day (LOAEL, mortality)** 100, 200, 300, 400, 500mg/kg	In a lethality study, male Swiss albino mice (15/group) were given a single i.p. injection of 100, 200, 300, 400 or 500 mg/kg phthalic acid in 10% DMSO diluted in phosphate buffered saline. Mice were monitored for 30 days. Endpoint evaluated included mortality and clinical signs of toxicity. At 500 mg/kg, 12/15 mice died (3 days after treatment). At 400 mg/kg, 8/15 mice died (22 days after treatment). No deaths were seen in the other dose groups. Signs of toxicity (loss of appetite and tardiness) were seen at 300 and 400 mg/kg groups, but these symptoms disappeared gradually (data not shown). The authors conclude the maximum tolerated dose to be 400 mg/kg.	Route of administration (i.p. injection) lacks human relevance	Mortality: High	Jha et al. 1998 1336719
None reported Mouse; BALB/cJ; Female	Injection 1 days Dose of phthalic acid administered to animals in dose group 2: 50 uL of 1064 ug/mL concentration = 53.2 ug/mouse; 53.2 ug/0.02 kg-bw mouse (avg BW of mouse) = 2.7 mg/kg-bw/day	**POD: 2.7 mg/kg/day (NOAEL, immune, body weight) (1064 ug/mL)** 0, 1064ug/mL	Groups of mice were administered ovalbumin via injection, alone or in combination with phthalic acid, and evaluated for the adjuvant effects of phthalic acid by determination of Ig levels in blood. Body weights were determined to evaluate systemic effects. "After the primary immunization [with 1 ug ovalbumin, alone or in combination with phthalic acid], the animals were given one or two booster injections sc in the neck region with 0.1 ug ovalbumin in 100 uL 0.9% saline, without adjuvant or test substance. The first booster injection was given 10 days after primary immunization, the second 5 days later". After treatment, blood was collected and assayed for content of ovalbumin-specific IgE and IgG1 by ELISA methods. Adjuvant effect was defined as a statistically significant increased level of antibody in the phthalic acid group compared to the ovalbumin control group. Phthalic acid did not induce changes in serum IgE or IgG1 levels or body weight. The NOAEL was 2.7 mg/kg/day (1064 ug/mL).	The only endpoints evaluated were Ig levels in blood and body weight, and only one dose of phthalic acid was tested. The methodology was designed similarly to dermal sensitization studies, with inclusion of a potentiating adjuvant prior to treatment with the chemical of interest (phthalic acid). A group without adjuvant exposure was not included.	Nutritional/ Metabolic, Immune/ Hematological : Medium	Larsen et al. 2003 673414

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Phthalic anhydride - Acute (less than or equal to 24 hr)

Guideline and Animal Species, Strain, Sex	Exposure Route and Exposure Duration	Study-wide POD and Dose/ Concentration(s)	Summary	Major Limitations	Principal Target Organs/Systems and OQD*	Citation and HERO ID
Adherence to guidelines was not specified. Rabbit; New Zealand White - [rabbit]; Both	Eye instillation single dose single dose	**POD: Uninformative- not suitable for POD determination** 0.1g	In an acute eye irritation study, six New Zealand White rabbits (4 female, 2 male) were exposed to 0.1 g test chemical ("MRD-ECH-79-15"; purity not reported) by instillation into the conjunctival sac of one eye. The test substance was identified as phthalic anhydride residue in a companion document that was submitted with the TSCA 8d submission (HERO 13028219). The other eye was not exposed, and the eyes were not washed after instillation. The cornea, iris, and conjunctiva were examined 1 hour and 4 hours after exposure, and then again 1, 2, 3, 4, and 7 days after instillation. Animals with positive irritation scores after 7 days were examined again on day 10. Animals with positive irritation scores on day 10 were examined on day 14. Corneal opacity was determined by fluorescein and cobalt blue staining. The eyes were graded by the Draize scoring system.Four out of six test animals had positive corneal scores, and all animals had positive iridal and conjunctival scores. Corneal irritation persisted through day 14 in three test animals. Iridal and conjunctival irritation persisted through day 14 in four test animals. The authors classified phthalic anhydride as an irritant based on these findings.	The test substance was identified as "MRD-ECH-79-15" in the study report. The test substance was identified as phthalic anhydride residue in a companion document that was submitted with the TSCA 8d submission (HERO 13028219). No further information was provided in either document indicating the composition and/or identity of the test substance.	Irritation: Uninformative	MB Research Laboratories Inc 1979 12980179

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Phthalic anhydride - Acute (less than or equal to 24 hr)

Guideline and Animal Species, Strain, Sex	Exposure Route and Exposure Duration	Study-wide POD and Dose/ Concentration(s)	Summary	Major Limitations	Principal Target Organs/Systems and OQD*	Citation and HERO ID
Adherence to a guideline was not specified. Rabbit; New Zealand White - [rabbit]; Both	Dermal 24 hours single dose	**POD: Uninformative- not suitable for POD determination** 3.16g/kg	In a dermal toxicity study, New Zealand White rabbits (2/sex) were exposed by dermal exposure to 3.16 g/kg of phthalic anhydride ("MRD-ECH-79-15"; purity not reported; dissolved in Mazola oil) by application to the abraded abdomen of each animal. The trunk of the animal was covered with gauze patches, adhesive tape, and impervious material, which was removed, along with residual test chemical, after 24 hours. Water or corn oil was used to wash the exposure site and remove excess test chemical. Animals were observed for mortality and signs of toxicity at 2 and 4 hours post dosing, and daily for 14 days. Body weight was recorded prior to dosing and at 14 days post dosing. Skin irritation was evaluated 1, 3, 7, 10, and 14 days after dosing and scored using the Draize scoring system. Gross necropsy was performed on all test animals at the conclusion of the study (organs not specified in methods; results reported for heart and anogenital). All test animals survived the exposure to 3.16 g/kg phthalic anhydride. Clinical signs observed included isolated instances of lethargy, ptosis, and diarrhea. There were no treatment-related effects on body weight reported. Severe erythema and moderate edema were reported test animals exposed to 3.16 g/kg. Gross necropsy findings were non-specific and included dilated heart and brown anogenital exudate.The authors classified phthalic anhydride as "non-toxic", based on a LD50 of greater than (>) 3.16 g/kg (>3160 mg/kg).	The test substance was identified as "MRD-ECH-79-15" in the study report. The test substance was identified as phthalic anhydride residue in a companion document that was submitted with the TSCA 8d submission (HERO 13028219). No further information was provided in either document indicating the composition and/or identity of the test substance. Test substance was applied to abraded skin.	Mortality, Irritation: Uninformative	MB Research Laboratories Inc 1979 12980180

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Phthalic anhydride - Acute (less than or equal to 24 hr)

Guideline and Animal Species, Strain, Sex	Exposure Route and Exposure Duration	Study-wide POD and Dose/ Concentration(s)	Summary	Major Limitations	Principal Target Organs/Systems and OQD*	Citation and HERO ID
Adherence to guidelines was not specified. Rat; Wistar - [rat]; Male	Oral: Gavage one days single dose	**POD: Uninformative- not suitable for POD determination** 1.0, 1.47, 2.15, 3.16, 4.64, 6.81g/kg	In an acute oral toxicity study, male Wistar rats (5/group) were exposed by gavage to a single test chemical dose ("MRD-ECH-79-15"; identified as "phthalic anhydride residue in HERO 13028219; purity not reported) of 1.0, 1.47, 2.15, 3.16, 4.64, and 6.81 g/kg. The study indicated that a higher dose group (10 g/kg) was included in the study, but data for this group is reported elsewhere (project number MB 79-3906), and therefore, is not included in this evaluation. Animals were observed for mortality and signs of toxicity at 1, 2, 4 and 6 hours post dosing, and daily for 14 days. Body weight was recorded prior to dosing and at 14 days post dosing. Gross necropsy was performed on all test animals at death or at the conclusion of the study (organs not specified in methods; results reported for anogenital, intestines, lungs, heart, and stomach). No animals died following exposure to $\leq$3.16 g/kg. Three animals died in the 4.64 g/kg group, and all five animals died in the 6.81 g/kg group. Predeath clinical signs included lethargy, chromodacryorrhea, ptosis, dyspnea, flaccid muscle tone, ataxia, bulging eyes, and prostration. There were no treatment-related effects on body weight reported. Gastrointestinal irregularities were noted during gross necropsy in animals that succumbed to exposure. Animals that survived exposure had no significant necropsy findings.The authors reported an acute oral LD50 of 3.15 g/kg (3150 mg/kg).	The test substance was identified as "MRD-ECH-79-15" in the study report. Another document in the TSCA 8d submission identified "MRD-ECH-79-15" as "phthalic anhydride residue". No further information was provided in either document indicating the composition and/or identity of the test substance.	Mortality: Uninformative	MB Research Laboratories Inc 1979 12980186

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Phthalic anhydride - Acute (less than or equal to 24 hr)

Guideline and Animal Species, Strain, Sex	Exposure Route and Exposure Duration	Study-wide POD and Dose/ Concentration(s)	Summary	Major Limitations	Principal Target Organs/Systems and OQD*	Citation and HERO ID
No guidelines were cited. Rat; Wistar - [rat]; Male	Oral: Gavage 1 days Single gavage	**POD: Uninformative - Study not suitable for POD determination.** 10g/kg	Male Wistar rats (n=5) were administered 10.0 g/kg of phthalic anhydride residue (identified as MB 79-3906 in report; reported in TSCA 8d, a compound of interest [HERO 13028219]) via gavage one time. The test substance was prepared as a 50% w/v mixture in distilled water. Rats were observed 1, 2, 4, and 6 hours after dosing and daily for 14 days. Endpoints evaluated included mortality, clinical signs, and gross necropsy. Four animals died on the first day and one on day 3. Clinical signs observed prior to death include lethargy, flaccid muscle tone, ataxia, piloerection, chromorhinorrhea, chromodacryorrhea, dyspnea, and ptosis. Gross necropsy observations included red areas on the intestines (2/5 rats) and bloated stomach (3/5 rats).Due to uncertainties of the test substance identity, the study is unsuitable for POD determination.	The test substance was identified as phthalic anhydride residue in HERO 13028219; no further information was provided indicating the composition of the test substance.	Mortality: Uninformative	MB Research Laboratories, Inc. 1979 12980187
Adherence to guidelines was not specified Rat; Wistar - [rat]; Male	Oral: Diet 34-36 days	**POD: 5,000 mg/kg/day (NOAEL, liver, kidney)** 0, 0.5, 5 % (in water or food)	The study does not report the food intake, body weight or age of rats. Default values were used for conversions.Food factor: Age of the rats was not reported. Based on cited reference, we are assuming the rats are ”about 320 g” which would make them about 8 weeks old (based on Animal Resources Center data). This was considered a young rat and therefore a food factor of 0.1 was used. The following formula was used to convert the percentage of chemical in food to mg/kg/day: % * 10,000 * food factor = mg/kg-bw/day.POD calculation: 5% * 10,000 * 0.1= 5,000 mg/kg/dayMale Wistar rats (5/group) were fed a powder diet containing 0, 0.5 or 5% phthalic acid for 34-36 days. Body weights were measured through out the study. Endpoint evaluated included serum biochemistry, organ weight (liver, kidney, spleen, testicle), histology (liver, kidney, testicle) and enzyme activity of succinate dehydrogenase (SDH), pyruvate dehydrogenase (PDH) and glutamate dehydrogenase (GLDH) in the liver. No significant difference in body weights were seen throughout the study or at the time of sacrifice. No changes in serum biochemistry were seen compared to control. Absolute and relative liver, kidney, spleen and testicle weights were not different from control. No abnormal histology was seen in the liver, kidney or testicle. Activities of SDH, PDH and GLDH in the liver were not different from control levels.	The study does not report the food intake, body weight or age of rats. Default values were used for conversions.	Reproductive/Developmental, Immune/Hematological, Hepatic/Liver, Nutritional/Metabolic, Renal/Kidney: Medium	Murakami et al. 1986 61568

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Phthalic anhydride - Acute (less than or equal to 24 hr)

Guideline and Animal Species, Strain, Sex	Exposure Route and Exposure Duration	Study-wide POD and Dose/ Concentration(s)	Summary	Major Limitations	Principal Target Organs/Systems and OQD*	Citation and HERO ID
No guideline or indication of GLP compliance reported. Rat; Sprague-Dawley - [rat]; Male	infusion 1 days Phthalic acid solution was infused for 2 minutes into nucleus basalis magnocellularis (NBM); allowed to diffuse into NBM for 2 additional minutes.300 ng PA dose in 0.5 ul vehicle converted to dose = 0.001 mg/kg based on rat bd wt of 300 g.	**POD: 0.001 mg/kg/day (LOAEL, neuro, bd wt)** 0, 300ng/0.5 ul	The nucleus basalis magnocellularis (NBM) of Sprague-Dawley rats were infused (infused for 2 minutes) with phthalic acid solution (300 ng PA dose in 0.5 ul vehicle (50% DMSO, 20, 0.9% saline, ~20% 5N NaOH [to pH 7.4] and ~10% ddH2O) to induce lesions in the NBM. 300 ng/0.5 ul = 0.001 mg/kg based on rat bd wt of 300 g. Rats infused with the vehicle solution only served as sham controls. Outcomes evaluated for PA-lesion rats and sham control rats included behavioral outcomes (unconditioned freezing behavior to fake or real cat hair, open field activity, freezing in shock context) and Body weight gain. PA-lesion rats had a significantly decreased display of freezing in the presence of cat hair compared to sham controls. None of the PA lesion rats showed freezing behavior in the shock context while 50% of sham rats did. There were significant effects on open field activity. PA-lesion rats had significantly decreased body weight gain 2 weeks post-infusion surgery. A LOAEL of 0.001 mg/kg was determined based on effects on unconditioned fear behavior and decreased body weight gain. A NOAEL was not established.	The study is designed as a mechanistic study to determine if removing cholinergic input (with drugs) to basolateral amygdala (BLA) with phthalic acid -induced lesions in nucleus basalis magnocellularis (NBM) alters rats' freezing behavior in presence of cat hair. infusion into the NBM was the route of exposure for phthalic acid; not a standard route of exposure	Neurological/Behavioral, Nutritional/Metabolic: Medium	Power and Mcgaugh 2002 6816161
No guidelines were cited. Rabbit; New Zealand White - [rabbit]; Unknown	Dermal 4 hours Test substance was applied to the skin for 4-hours and then washed off.	**POD: Non-corrosive to the skin** 0.5gram	In a dermal corrosion study, New Zealand Albino rabbits (n=6; sex not reported) had their hair clipped from their trunks. 0.5 grams of phthalic anhydride was applied as a paste to the skin, covered with a gauze patch and secured with an adhesive tape (phthalic anhydride flakes were uniformly mixed with water to form a 58.6% paste). The truck was wrapped with rubberized elastic cloth to retard evaporation and maintain the test patch position. After 4 hours, the patch was removed, and the test site was washed. Corrosion readings were made at 4 hours and 48 hours after exposure. The test substance was considered corrosive if it caused destructive or irreversible alteration of the tissue (ulceration or necrosis). Epidermal sloughing, erythema, edema or fissuring were not considered tissue destruction. No remarkable findings were observed. The test substance was not considered a corrosive agent.	Sex, age and body weights were not reported.	Irritation: Medium	Product Safety Labs, 1982 12980188

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Phthalic anhydride - Acute (less than or equal to 24 hr)

Guideline and Animal Species, Strain, Sex	Exposure Route and Exposure Duration	Study-wide POD and Dose/ Concentration(s)	Summary	Major Limitations	Principal Target Organs/Systems and OQD*	Citation and HERO ID
The study was conducted to comply with GLP regulations. The study followed OECD guideline 403 and Methods for the Determination of Toxicity and Other Health Effects, Part B.2 (Acute 'toxicity Inhalation) Council Regulation (EC) No. 440/2008. Rat; Sprague-Dawley - [rat]; Both	Inhalation: Aerosol 4 hours 4-hour inhalation exposure	**POD: LC50 >2.14 mg/L** 2.14mg/L	In an acute toxicity study, Sprague-Dawley rats (5/sex) were exposed to 2.14 mg/L (maximum attainable exposure levels) of phthalic anhydride via nose-only inhalation for 4 hours. Animals were observed for 14 days post-exposure. Endpoints evaluated include mortality, clinical signs of toxicity, behavioral changes, body weights (initial, and days 7 and 14), and gross necropsy. One male died after the 4-hour exposure; no clinical signs or behavior changes were observed in this male prior to death. All other animals survived the 14-day observation period. Clinical signs observed in animals the first days after exposure include hypoactivity, irregular respiration, moist rales, reduced fecal volume, ocular discharge, dyspenea, facial staining, and ano-genital staining (females only). These effects resolved after a couple of days. All animals were active and healthy 3-7 days (males) or 4-9 days (female) after exposure, except for one female that continued to have facial staining up to day 13. All males gained weight over the study period. Three/five females lost weight by day 7, but overall, gained weight over the 14-day observation period. Gross necropsy of the male that died early showed discoloration of the lungs and liver. No gross abnormalities were noted in any animal that survived the 14-day observation period. The author reported LC50 is >2.24 mg/L.	Respiratory rates were not monitored, and the test chemical is a respiratory irritant. No other major limitations were identified. This was a well-reported study following OECD test guidelines.	Mortality, Lung/Respiratory: High	Eurofins PSL 2010 12980171
None reported. Guinea pig; Hartley - [guinea pig]; Female	subcutaneous Animals were injected subcutaneously with phthalic acid in olive oil 2 times/week for 4 weeks. After one week of rest, animals were reinjected once with the same dose of phthalic acid. Animals were allowed to rest for another week and then tested for immune reactivity.	**POD: Negative for sensitization** 0, 0.00067Molar	See footnotes for full summary [4]	The study was unable to conduct challenges with phthalic acid.	Sensitization: Medium	Sarlo and Clark 1992 65818

* Overall Quality Determination

[1] 12980183: In a dermal irritation study, New Zealand White rabbits (3/sex) had the dorsal surface from the shoulder region to the lumbar region closely clipped. The next day, 0.5 g of phthalic anhydride undiluted (reported in reference as MRD-87-113 but identified in HERO 13028219 as the compound of interest) was applied to the clipped dorsal surface and covered with a gauze patch held in place with occlusive tape (Day 0). After approximately 4 hours, the gauze was removed, and residual test material was removed using distilled water and paper towels. A second virgin site on the dorsal surface was clipped on Day 6, the next day, 0.5 gram of test substance moistened with 0.5 ml of saline was applied to the site with an occlusive dressing for 4 hours. After 4 hours, the gauze was removed and the test site was washed as described previously. Animals were examined for mortality 1-2 times/day, body weights were recorded on the first day of dosing (day 0), day 7 (first day of 2nd site dosing) and day 14. Dermal response was evaluated at both sites approximately 45 minutes, 24 hours, 48 hours, 72 hours, and 7 days after the patch was removed. Draize Method of Scoring was used to assess irritation. All animals survived the entirety of the study. All animals gained weight through the study period. Application of the neat test substance resulted in slight erythema (score of 1) in one female at 45 minutes, 24, 48, and 72 hours. The effect was reversible by day 7. No irritation was observed in any other animal following neat application. Application of the moistened test substance resulted in very slight erythema in one animal, and very slight to well-defined erythema (scores of 1 and 2, respectively) in the remaining animals. Reversal was not achieved in 5/6 animals (scores still 1) by observation day 7. Very slight to slight edema was observed in 4/6 animals at 45 minutes and 24 hours; and in 2/4 animals at 48 hours following application of moistened test substance. At 72 hrs and at 7 days, edema was no longer observed at the application site. Mean erythyma and edema scores (at 24, 48, and 72 hrs) were not provided, but can be calcuated based on the data provided. Brown/black staining was also observed at the application site in all animals at 45 minutes and in 5/6 animals at 24 and 48 hours. At 7 days, only 1/6 animals still had staining.The primary irritation index was calculated to be 0.17.The primary irritation index for the moistened test substance was 2.00.The study authors reported that the test substance was a ”very mild irritant when used neat, but a moderate irritant when moistened.”

[2] 5177461: Groups of male and female Dunkin-Hartley guinea pigs (7-8/group, sex distribution not specified) were sensitized by single intradermal 100uL volume injections of 0, 0.03, 0.1, and 0.3% phthalic anhydride (PHA) in 6% acetone in corn oil into the scapular region on study day 1. Control animals were injected with vehicle only. On study day 22, animals were subjected to an inhalation challenge exposure. PHA was freshly ground just prior to use and animals were exposed nose-only to challenge concentrations of 11-29 mg PHA dust/m3 in an argon atmosphere or PHA dust concentrations of 9-48 mg/m3 in dry air for 15 minutes. Control animals were exposed to each atmosphere (air-only) alone. Particle sizes and distributions were apparently determined, but values were not reported. Animals were monitored constantly for respiratory stress and respiratory rates were monitored during pre-challenge (10 min prior to challenge), and during the challenge and during recovery (a 15-min period post-challenge, or until breathing returned to background levels). Serum samples were collected from animals on study day 19 for measurement of PHA specific IgG1 antibodies using ELISA and passive cutaneous anaphylaxis (PCA) analysis. Both ELISA and PCA analysis showed serum samples from PHA sensitized animals contained PHA-specific antibodies; the control responses were appropriate. In the argon atmosphere, pulmonary reactions were observed in 2/8, 2/8, 2/7 and 4/8 animals in the 0, 0.03%, 0.1%, and 0.3% induction groups, respectively. In the 3% induction group, the reactions were considered severe in all 4 cases. One severe case occurred in all other groups, including controls. In the dry-air atmosphere, pulmonary reactions were observed in 0/8, 1/7, 1/8 and 3/8 animals in the 0, 0.03%, 0.1%, and 0.3% induction groups, respectively. All observed reactions were considered to be severe. Responses observed in groups sensitized with lower concentrations were thought to be due to an irritant response.Phthalic anhydride is a respiratory sensitizer in guinea pigs intradermally sensitized to phthalic acid and challenged via inhalation.

[3] 5177461: Male and female Dunkin-Hartley guinea pigs (8 controls and 12 treatment animals, sex distribution was not specified) were sensitized by a single intradermal 100uL volume injection of 0.3% phthalic anhydride (PHA) in 6% acetone in corn oil into the scapular region on study day 1. Control animals were injected with vehicle only. On study day 22, animals were subjected to an inhalation challenge exposure. PHA was generated as a dust and animals were exposed nose-only to air-only (controls) or an atmosphere containing 44 mg PHA/m3 for 15 minutes. Particle sizes and distributions were determined, but values were not reported. Animals were monitored constantly for respiratory stress and respiratory rates were monitored during pre-challenge (10 min prior to challenge), and during the challenge and during recovery (a 15-min period post-challenge, or until breathing returned to background levels). Serum samples were collected from animals on study day 19 for measurement of PHA specific IgG1 antibodies using ELISA and passive cutaneous anaphylaxis (PCA) analysis. Both ELISA and PCA analysis showed serum samples from PHA sensitized animals contained PHA-specific antibodies; the control responses were appropriate. No pulmonary reactions occurred in any treatment animals following the inhalation challenge. A problem with the procedure for the generation of the test atmosphere was identified (see below under major limitations); modifications were made and the experiment was repeated: In the second experiment, male and female Dunkin-Hartley guinea pigs (7 controls and 12 treatment animals, were similarly sensitized by a single intradermal 100uL volume injection of 0.3% phthalic anhydride (PHA) in 6% acetone in corn oil into the scapular region on study day 1. Control animals were injected with vehicle only. On study day 22, animals were subjected to an inhalation challenge exposure, this time with freshly ground PHA, animals were exposed nose-only to a dry-air atmosphere containing air-only (controls) or 52 mg PHA dust/m3 for 15 minutes. Animals were monitored as described. A pulmonary reaction was observed in 8/12 exposed animals vs. 1/7 controls. The reactions were considered severe in 7 exposed animals and moderate in one exposed animal. These were expected results for phthalic anhydride. Statistical analyses were not performed. A Fisher's exact test (two-tailed) conducted for this review, results in a p-value of 0.057, which is borderline significant. Phthalic anhydride is a respiratory sensitizer in guinea pigs intradermally sensitized to phthalic acid and challenged via inhalation.

[4] 65818: Female Hartly smooth-haired guinea pigs (10/group) were subcutaneously injected with 400 uL of 0 or 6.7 x10-4 M phthalic acid in olive oil 2 times/week for 4 consecutive weeks. After a 1-week rest period, animals were reinjected with 400 uL of either control or phthalic acid at the respective dose. Animals were allowed to rest for an additional week before being evaluated for immune reactivity via three separate tests: a passive cutaneous anaphylaxis (PCA) test, and intratracheal challenge, and an active cutaneous anaphylaxis (ACA) skin test. For all tests, a phthalic anhydride (PA)- guinea pig serum albumin (GPSA) conjugate was used as the antigen because the authors could not generate a phthalic acid conjugate. In the respiratory reactivity test, 100uL of a PA-GPSA conjugate (500 ug/ml of conjugate based on protein) was delivered to the tracheal bifurcation. Changes in breathing pattern were monitored visually for 10 minutes following the challenge. "A significant respiratory reaction was defined as diaphragmatic contractions occurring at a minimum of every 36 to 40 normal breaths occurring over an observation period of 10 min." For ACA skin test: Forty-eight hours after guinea pigs were intratracheally challenged, the same guinea pigs were anesthetized and intracardially injected with 1 mL of 0.1% Evans blue dye in saline. Thirty minutes later, these animals were intradermally injected with 50 uL of 0.04, 0.4, 4, 40, or 400 ug/mL of PA-GPSA or GPSA alone. It was not specified how many animals were injected with each concentration, or if all animals were injected with all concentrations at different sites. Visible bluing at the antigen injection site was considered a positive response (identification of IgG1a and/or IgE). Passive cutaneous anaphylaxis (PCA) testing was performed to determine IgG1a antibody titers. Naïve guinea pigs were intradermally injected with 100-ul of sera (collected at day 1 following end of the initial exposure period) diluted 1/5 to 1/2560 in saline. Four hours later, anesthetized animals were intracardially injected with 1.0 ml of 500 ug/ml antigen (PA-GPSA or GPSA) in a 1% Evans blue dye isotone solution. Sera IgG1a titers were determined 30 minutes following intracardial injectionNo Respiratory reactivity or skin reactivity were seen in any of the animals initially dosed with phthalic acid or control animals. No antibody titers were seen in the sera after the injection period ended or in the PCA test. Phthalic acid did not sensitize animals to PA-GPSA at 6.7 x 10^-4 M.

Phthalic anhydride - Short-term (>1-30 days)

Guideline and Animal Species, Strain, Sex	Exposure Route and Exposure Duration	Study-wide POD and Dose/ Concentration(s)	Summary	Major Limitations	Principal Target Organs/Systems and OQD*	Citation and HERO ID
No guidelines or use of GLP practices were reported. Rat; Sprague-Dawley - [rat]; Both	Inhalation: Aerosol 6 hours/day 5 days Animals were exposed via inhalation 6 hrs/day for 5 days. After a 3 week resting period, animals were challenged with a single 6 hour exposure. It was not specified that exposure was to a vapor. Vapor was selected above because a selection is required.**Additional information available in the associated reference (HEROID 12980190) provides additional information such as this study uses an aerosolized version of phthalate anhydride (PA). Selection is corrected above to note an aerosol was used.	**POD: Positive for respiratory sensitization in rats following inhalation sensitization and challenge.** 0, 500ug/cm3	See footnotes for full summary [1]	Data were presented in a letter and is not a full study report. It was indicated that the results reported were preliminary and based on verbal reports from laboratory personnel. Limited details were provided and this data is considered unreliable.**Additional information available in the associated reference (HEROID 12980190) provides additional information such as the experimental design and more detailed results. However, there is no detailed information on the purity of the test substance and even with the report, there are still missing details dealing with the animals, such as husbandry. Additionally, there is no statistical data described, yet there are statistically significant increases in serum IgG reported in this study.	Lung/Respiratory, Sensitization: Uninformative	Amoco. 1988 5160442
Non-guideline, methods development study. Adherence to GLP conditions was not specified. Mouse; Balb/c - [mouse]; Male	Inhalation: Aerosol 6 hours/day 3 days Exposure groups were exposed for 45, 90, 180, or 360 min/day for three consecutive days.	**POD: 63 µg (ED3, respiratory sensitization)** 0, 14.2 mg/m^3	See footnotes for full summary [2]	Data were not adequately reported for non-sensitization endpoints. Respiratory irritation, potentially leading to bradypnea, was identified as a confounding factor. The study did not report whether animals were acclimated to nose-only exposure conditions.	Sensitization: Medium, Nutritional/Metabolic: Uninformative, Lung/Respiratory: Uninformative	Arts et al. 2008 1222879

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Phthalic anhydride - Short-term (>1-30 days)

Guideline and Animal Species, Strain, Sex	Exposure Route and Exposure Duration	Study-wide POD and Dose/ Concentration(s)	Summary	Major Limitations	Principal Target Organs/Systems and OQD*	Citation and HERO ID
Adherence to a guideline or to GLP conditions was not specified. Mouse; Balb/c - [mouse]; Male	Dermal 3 days The test substance (25% wt/vol) was applied once a day on three consecutive days.	**POD: 536 µg (EC3, dermal sensitization)** 25%	The purpose of this study was to develop a respiratory LLNA protocol and specifically, to determine whether inhalation allergens could induce proliferation in lymph nodes, and to test if the potency of responses is comparable between dermal and inhalation routes. Several known respiratory allergens, including phthalic anhydride, and contact allergens were used. A standard skin LLNA assay (described here) was used as a positive control for the respiratory LLNA protocol. In a standard LLNA assay, 25 µl/day of a test solution contining 25% (wt/vol) phthalic anhydride (purity ≥99%) was applied to the dorsum of both ears of male BALB/c mice (3/group) daily for three consecutive days. The test solution contained phthalic anhydride dissolved in a 4:1 mixture of acetone and olive oil. Control animals received dermal applications of acetone-olive oil alone. Animals were necropsied on day 5, and auricular lymph nodes were excised, and proliferation was assessed ex vivo using [3H]thymidine labeling. To assess the ability to distinguish between respiratory and contact sensitizers, cytokine production was assessed in local lymph node cells after cultivation with concanavalin A (5 ug/mL) for 24 hours (results reported in HERO 652441). Other methodological details of the dermal experiment were limited, and the endpoints assessed beyond local lymph node proliferation and cytokine are unclear (results for other potential endpoints are not reported). Stimulation index (SI) ≥ 3 indicates a positive response in the skin LLNA assay. The mean ± SEM SI in auricular LN was 93 ± 21, indicating the test substance was positive for dermal sensitization. The authors calculated an EC3 value of 546 ug, representing the concentration which induces stimulation rates 3-fold above control.	There is ambiguity in the endpoints that were evaluated in this study. The biological response of the negative control group was not reported.	Sensitization: Medium	Arts et al. 2008 1222879
No guideline or GLP conditions were reported. Mouse; Not specified; Unknown	Dermal 3 days/week 3 weeks 50 ul of test substance was applied to the dorsum of the ear 3 times a week for 3 weeks.	**POD: Positive (allergic skin response)** 0, 1, 5, 10%	See footnotes for full summary [3]	Statistical analysis was not adequately reported. The lack of sample sizes precludes the ability to conduct independent statistical analysis. Information on animals and animal husbandry conditions was not adequately reported.	Sensitization: Medium	Bae et al. 2011 5177984

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Phthalic anhydride - Short-term (>1-30 days)

Guideline and Animal Species, Strain, Sex	Exposure Route and Exposure Duration	Study-wide POD and Dose/ Concentration(s)	Summary	Major Limitations	Principal Target Organs/Systems and OQD*	Citation and HERO ID
No guideline or GLP conditions were reported. Mouse; Not specified; Unknown	Dermal 3 days/week 3 weeks 50 ul of test substance was applied to the dorsum of the ear 3 times a week for 3 weeks.	**POD: Positive (allergic skin response)** 0, 1, 5, 10%	See footnotes for full summary [4]	Statistical analysis was not adequately reported. The lack of sample sizes precludes the ability to conduct independent statistical analysis. Information on animals and animal husbandry conditions was not adequately reported.	Sensitization: Medium	Bae et al. 2011 5177984
Adherence to a guideline was not specified. Mouse; Balb/c - [mouse]; Female	Dermal 4 days Mice received a dermal application of 50ul a 12% phthalic anhydride (450 mg/kg)) or vehicle on their shaved flanks on day 0. On day 7 mice were challenged by the application of vehicle or 6.25% phthalic anhydride (234 mg/kg) on the the dorsum of both ears	**POD: Positive for dermal sensitization** 12.5, 6.25%	See footnotes for full summary [5]	There were limitations regarding exposure characterization, including the unclear nature of when the challenge occurred; authors provide enough information to ascertain that it was after 7 but before day 11 of the study. Additionally, the study only examined one dose of phthalic anhydride (12.5%) for the sensitization phase via intradermal injection, which limits its utility for dose-response evaluation	Sensitization: High	Ban and Hettich 2004 83939
No guidelines were reported; however, the study design is similar to LLNA OECD 429. The study did not report GLP compliance. Mouse; CBA/Ca; Unknown	Dermal 3 days Animals were exposed for 3 consecutive days	**POD: Positive for skin senstization in an LLNA assay** 0, 2.5, 5, 10%	In a LLNA study, CBA/Ca mice (4/group; sex not reported) had 25ul of 2.5%, 5% or 10% phthalic anhydride (purity not reported; in 4:1 acetone:olive oil [AOO]); or AOO (control) applied to the dorsum of both ears for 3 consecutive days. The next day, mice were injected (i.v.) with 3H-thymidine. Five hours later, auricular lymph nodes were collected to assess proliferation by determining 3H-thymidine incorporation. The test substance was considered a sensitizer if lymphocyte proliferation was threefold greater than control. The ratios of test substance to control lymphocyte proliferation were 26.0, 21.5, and 20.9 at 2.5%, 5%, and 10% respectively.The test substance was considered positive for sensitization, but no dose response was observed.	Purity and husbandry conditions were not reported. Negative control data were not shown.	Sensitization: Medium	Basketter et al. 1992 5353562

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Phthalic anhydride - Short-term (>1-30 days)

Guideline and Animal Species, Strain, Sex	Exposure Route and Exposure Duration	Study-wide POD and Dose/ Concentration(s)	Summary	Major Limitations	Principal Target Organs/Systems and OQD*	Citation and HERO ID
The study was similar to Magnusson and Kligman (1970). The study did not report whether it was GLP-compliant. Guinea pig; Albino Dunkin-Hartly; Unknown	Dermal 4 days Animals were given six intradermal injections of 0.1% phthalic anhydride into the shoulder region. After 6-8 days, an occluded patch containing 25% phthalic anhydride was placed on the injection site for 48 hours. Twelve to fourteen days later, animals were challenged on one flank by a 24-hour occluded patch containing 10% phthalic anhydride.	**POD: Positive for skin sensitizaiton in a GPMT** 0.1%	In a guinea pig maximization test, Albino Dunkin-Hartly guinea pigs (number of animals was not reported) were given a series of six intradermal injections of 0.1% phthalic anhydride (purity not reported; in 0.9% NaCl, aided by acetone if necessary) into the shoulder region. After 6-8 days, an occluded patch containing 25% phthalic anhydride (vehicle was acetone-polyethylene glycol 400 (70:30, v/v) was placed on the injection site for 48 hours. Twelve to fourteen days later, animals were challenged on one flank by a 24-hour occluded patch containing 10% phthalic anhydride (maximum non-irritant concentration; vehicle was acetone-polyethylene glycol 400 (70:30, v/v). Challenge sites were scored for erythema (scale 0-3) and edema 24 and 48 hours after the removal of the patch. Limited methodological details were provided, including the use of controls, although the authors stated that the study was carried out in a manner similar to those described in Magnusson B. and Kligman A. M. (1970) The percentage of animals judged to be positive at 24 and/or 48 hours was 90%. No further results were provided. The test substance was considered an extreme sensitizer.	It is unclear if a negative control group was included. Limited details on methods were provided.	Sensitization: Uninformative	Basketter et al. 1992 5353562
The study used the standard Buehler test and and a modified version of Buehler test for skin sensitization (OECD 406). Guinea pig; Hartley - [guinea pig]; Both	Dermal 6 hours/day 1 days/week 4 weeks Induction phase: animals were exposed for 6 hours/day, once a week for 3 weeks (days 3, 10, and 17). Animals were allowed to rest for 11 days and then were challenge on day 29.	**POD: Positive for skin sensitization** 0, 20%	See footnotes for full summary [6]	None	Sensitization: High	Botham et al. 2005 5177112

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Phthalic anhydride - Short-term (>1-30 days)

Guideline and Animal Species, Strain, Sex	Exposure Route and Exposure Duration	Study-wide POD and Dose/ Concentration(s)	Summary	Major Limitations	Principal Target Organs/Systems and OQD*	Citation and HERO ID
The study used the standard Buehler test as well as a modified version of Buehler test for skin sensitization (OECD 406). Guinea pig; Hartley - [guinea pig]; Both	Dermal 18 days Induction phase: Exposures varied with concentration on different days of the induction phase and consisted of 20% phthalic anhydride on days 1, 3, 5, and 8, and 10% phthalic anhydride on days 10, 12, 15, 16 and 17. Animals were allowed to rest for 11 days and then challenged with on day 29 with 20% phthalic anhydride for 6 hours.	**POD: Positive for skin sensitization** 0, 20%	See footnotes for full summary [7]	None	Sensitization: High	Botham et al. 2005 5177112
Study does not report following a guideline or GLP practices. The study is similar to an OECD 414 study, although there are several deviations. Rat; Wistar Kyoto (WKY) - [rat]; Female	Oral: Diet 10 days Pregnant females were exposed via diet from GDs 7-16	**POD: 1,021 mg/kg/day (NOAEL, changes in body weight gain and food consumption)** 0, 1021, 1763, 2981 mg/kg-bw/day	No maternal deaths or clinical signs were observed. Bodyweight changes appeared to reflect changes in food consumption. Food consumption and body weights were statistically significantly decreased by 13% and 18% at the mid-dose and 27% and 59% at the high dose respectively, during the days of treatment (GDs 7-16). It was not indicated whether this was due to palatability issues. After treatment (GDs 16-20), treated animals from all dose groups showed significant dose-related increases in food consumption, relative to controls and similar increases in body weight gain were observed (14% greater than controls at 1763 mg/kg-day: not statistically significant, and 39% greater than controls at 2981 mg/kg-day). The adjusted weight gain (minus gravid uterine weight) of females was decreased in a dose-related manner (6%, 16%, and 40% in the low, mid, and high groups, respectively, compared with controls), reaching significance at the high dose. The maternal body weight gain on days 7–16 in the 2.5 and 5.0% groups and the adjusted weight gain, which indicates the net weight gain of maternal rats, in the 5.0% group were significantly lower than those in the control group.	Although generally well-conducted, this study has several limitations. First, it included fewer dams per dose group than recommended by current OECD TG No. 414 (11 vs. 20 dams per dose group). Second, the exposure window did not cover late gestation up to parturition, as recommended by current OECD TG No. 414 {OECD, 2018, 5381356}.	Nutritional/Metabolic: High	Ema et al. 1997 790543

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Phthalic anhydride - Short-term (>1-30 days)

Guideline and Animal Species, Strain, Sex	Exposure Route and Exposure Duration	Study-wide POD and Dose/ Concentration(s)	Summary	Major Limitations	Principal Target Organs/Systems and OQD*	Citation and HERO ID
Study does not report following a guideline or GLP practices. The study is similar to an OECD 414 study, although there are several deviations. Rat; Wistar Kyoto (WKY) - [rat]; Female	Oral: Diet 10 days Pregnant females were exposed via diet from GDs 7-16	**POD: 2,981 mg/kg/day (NOAEL, no effects at the highest dose tested)** 0, 1021, 1763, 2981 mg/kg-bw/day	Pregnant Wistar rats (11/group) were fed diets containing 0, 1.25, 2.5, or 5.0% phthalic acid from gestation day (GD) 7-16 of pregnancy. Reported intakes were 0, 1021, 1763, and 2981 mg/kg-day based on body weight and food intake data. The only statistically significant developmental effects occurred in the highest-dose group, which was also maternally toxic and included a 4% statistically significant decrease in male fetal body weights and a 7% decrease in ossification centers of caudal vertebrae in the treated fetuses, compared with controls. These effects were observed at a dose that resulted in a 59% reduction in maternal weight gain. PA was not teratogenic. The authors concluded the developmental NOAEL was 2981 mg/kg-day based on the lack of developmental toxicity observed, however, EPA should rereview to determine if it should be lowered because the exposure window was shorter than the current guideline standards, and may have missed the important developmental window for the skeletal effects, which are an effect of concern for chelators.	Although generally well-conducted, this study has several limitations. First, it included fewer dams per dose group than recommended by current OECD TG No. 414 (11 vs. 20 dams per dose group). Second, the exposure window did not cover late gestation up to parturition, as recommended by current OECD TG No. 414 {OECD, 2018, 5381356}.	Reproductive/Developmental: High	Ema et al. 1997 790543
The study did not follow a specific guideline, or GLP practices. Mouse; Balb/c - [mouse]; Female	induction applications (dermal); challenge (intratracheal) 9 days Animals received dermal induction applications of 25 ul of 0.3% PA in solvent (4:1 acetone:olive oil) 9 times (days 1-3, 8-10, and 15-17). An intratracheal challenge injection (0.03% PA in acetone, diluted in PBS) was administered on day 31.	**POD: Positive for respiratory sensitization in mice dermally sensitized to phthalic anhydride and intratracheal challenged.** 0, 0.3, 0.03% in solution	See footnotes for full summary [8]	Phthalic anhydride was included in the study as a known respiratory allergen for purposes of validating and determining the sensitivity of a method for detecting and testing for respiratory allergens.	Sensitization: High	Fukuyama et al. 2010 1940789
No guidelines were cited. Rat; Sprague-Dawley - [rat]; Both	Inhalation: Aerosol 6 days Animals were sensitized to 525 µg/m3 phthalic anhydride (PA) 6 hours/day for 5 days. Animals were allowed to rest for 3 weeks and then challenged with 481 µg/m3 phthalic anhydride for 6 hours.	**POD: Uninformative - the study is not suitable for POD determination.** 0, 525um/m3	See footnotes for full summary [9]	The study lacked appropriate controls, resulting in the study being uninformative. Purity and husbandry conditions were not reported. MMAD, particle size and GSD were not reported. The study lacked details of exposure (e.g., number of animals/cage, air changes etc.).	Sensitization: Uninformative	IIT Research Institute, 1996 12980190

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Phthalic anhydride - Short-term (>1-30 days)

Guideline and Animal Species, Strain, Sex	Exposure Route and Exposure Duration	Study-wide POD and Dose/ Concentration(s)	Summary	Major Limitations	Principal Target Organs/Systems and OQD*	Citation and HERO ID
No guideline stated. Mouse; Swiss albino; Male	intraperitoneal 5 days	**POD: 40 mg/kg/day (LOAEL, reproduction)** 0, 40, 80mg/kg	In a dominant lethal mutation study, male Swiss albino mice (20/group) were administered 0, 40 or 80 mg/kg/day phthalic acid in 10% DMSO diluted in phosphate buffered saline for 5 consecutive days. After treatment ended, each male was caged with 2 untreated females. Each week the females were replaced with 2 new untreated females; this was done for a total of 4 weeks. The time interval and mating schedule was chosen to distinguish postmeiotic (1-21 days) and meiotic (22-28 days) stages of spermatogenesis. Females were checked daily for copulation plug. On gestational day 14-16, females were sacrificed and uterines were examined for total, live and dead implants. Dominant lethality % was calculated by [1-(live implants per female in experimental group/live implants per female in control group) x 100]. No significant difference in the percentage of pregnant females or total, live or dead implants were seen in mice mated one week after treatment compared to control. The percentage of pregnant females significantly decreased at 40 mg/kg/day (week 3, 15%) and at 80 mg/kg/day (week 2: 15%; week 3: 30%; week 4: 30%). Significant decreases in total implants were seen at 40 mg/kg/day (week 3: 30%) and 80 mg/kg/day (week 2: 22%, week 3: 45% and week 4: 38%) compared to control. Implants/ female were significantly decreased at 40 mg/kg/day (15%) and 80 mg/kg/day (24%) at week 3 compared to control. Significant decreases in the live implants/female and significant increases in dead implants/female were seen at 40 mg/kg/day (week 3) and 80 mg/kg/day (week 2, 3 and 4). Dominant lethality increased in a dose-related manner at all timepoints and was maximal at week 3 (25.12% and 35.2%) at 40 and 80 mg/kg/day, respectively.	Effects on food consumption, body weight gain, clinical signs not evaluated. Route of administration (i.p. injection) lacks human relevance	Reproductive/Developmental: High	Jha et al. 1998 1336719

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Phthalic anhydride - Short-term (>1-30 days)

Guideline and Animal Species, Strain, Sex	Exposure Route and Exposure Duration	Study-wide POD and Dose/ Concentration(s)	Summary	Major Limitations	Principal Target Organs/Systems and OQD*	Citation and HERO ID
No guidelines or adherence to GLP were reported. Rat; Sprague-Dawley - [rat]; Male	Oral: Gavage 14 days Animals were gavaged once daily for 14 days. Gavage volumes were not reported.	**POD: 250 mg/kg/day (LOAEL, decreased body weight in male rats)** 0, 250 mg/kg-bw/day	In a short-term repeat-dose toxicity study, groups of Sprague-Dawley rats (5-6 males/group) were administered 0 (vehicle) and 250 mg phthalic acid (PA) in corn oil, daily via gavage, for a total of 14 days. Animals were observed daily for mortality and clinical signs of toxicity. Body weights were recorded on study days 0, 3, 6, 9, 12, and 14. Food consumption was measured at the beginning of the study and twice during treatment. Other endpoints included hematology, clinical chemistry, urinalysis, and organ weights (relative) included the lung, heart, liver, kidney, adrenal glands, spleen, thymus, thyroid, testes, and epididymides. No macroscopic or microscopic examinations were performed. No mortalities were observed, salivation was reported immediately after dosing, but it is unclear if results applied to PA because the data aren't shown. Body weights (displayed graphically) were statistically significantly decreased on study days 12 and 14 (decreases of approximately 13-14%, compared with controls, respectively). Food consumption (data not shown) was comparable between treatment groups and controls. No hematological, serum chemistry or organ weight changes were observed. Urinalysis showed an increase in leukocytes; however, the significance of this is unclear. A LOAEL of 250 mg/kg-day was determined based on decreased body weights in male rats administered PA via gavage for 14 days. This study also evaluated DEHP, DBP, DnOP, DEP, BBP, DMP, DIDP, DUP, DINP, MEHP, MBuP, MBeP, MEP, and MMP	Use of a single dose precludes the ability to evaluate a dose-response.Some methodological details were missing (gavage volume not reported).	Immune/Hematological: High, Hepatic/Liver: High, Nutritional/Metabolic: High, Renal/Kidney: High	Kwack et al. 2010 792143

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Phthalic anhydride - Short-term (>1-30 days)

Guideline and Animal Species, Strain, Sex	Exposure Route and Exposure Duration	Study-wide POD and Dose/ Concentration(s)	Summary	Major Limitations	Principal Target Organs/Systems and OQD*	Citation and HERO ID
No guidelines or adherence to GLP were reported Rat; Sprague-Dawley - [rat]; Male	Oral: Gavage 4 weeks	**POD: 250 mg/kg/day (LOAEL, bd wt, reproductive)** 0, 250 mg/kg-bw/day	In a 4-week repeat-dose study, male Sprague-Dawley rats (number not specified) were orally administered phthalic acid at doses of 0 (corn oil, vehicle control) and 250 mg/kg/day. Endpoints (evaluated in 6 animals/group) included mortality, clinical signs, food consumption, body weight, hematology (WBC, RBC, Hb, Ht, MCV, MCH, MCHC, PLT), biochemical serum analysis (GLU, T.P., ALB, GOT, GPT, ALP, CHO, HDL, GGT, TG, CA, BUN), urinalysis (occult blood, pH, protein, urobilinogen, glucose, nitrite, bilirubin, ketone bodies, leukocytes, urine specific gravity), organ weight measurements (thymus, heart, liver, spleen, kidney, adrenal, testis, epididymis), and sperm analysis (sperm count, motility, VAP, VSL, VCL, ALH, BCF, STR, LIN). There was a significant decrease in body weight starting at week 2 in treated rats (250 mg/kg/day) compared to controls. It is reported that leukocytes were change in the treated group; however, the change is unspecified and the data were not shown. A significantly decreased curvilinear velocity (VCL) in sperm of treated rats was reported when compared to controls. There were no other significant finding in any other endpoint evaluated. A LOAEL of 250 mg/kg/day (only dose tested) was determined based on decreased body weight and decreased VCL. A NOAEL was not determined. The study was designed to compare systemic toxicity and sperm parameters among selected phthalate esters (DEHP, DBP, DnOP, DEP, BBP, DIDP, DMP, DUP, DINP) and monoesters (MEHP, MBuP, MBeP, MEP, MMP) and phthalic acid.	The number of animals per study group were not specified. Data for mortality were not reported. There was no histopathology for organs evaluated. use of a single dose precludes the ability to evaluate a dose-response. Some methodological details were missing (gavage volume not reported)	Cardiovascular: High, Reproductive/Developmental: High, Nutritional/Metabolic: High, Immune/Hematological: Medium, Hepatic/Liver: Medium, Mortality: Medium, Renal/Kidney: Medium	Kwak et al. 2009 697382
Adherence to a test guideline or GLP were not specified. Rat; Wistar - [rat]; Male	Oral: Gavage 7 days DEHP was administered via gavage, but it was not specified if phthalic acid was also administered via gavage.	**POD: 850 mg/kg bw/day (NOAEL, liver)** 0, 850 mg/kg-bw/day	Young (age not specified), male Wistar albino rats (6/group) were orally administered 1,2-phthalic acid at 0 and 850 mg/kg bw/day. Negative controls were administered corn oil. Endpoints evaluated included liver weight, biochemistry (succinate dehydrogenase, glucose-6-phosphatase, aniline 4-hydroxylase, biphenyl 4-hydroxylase, cytochrome P-450, and microsomal protein), and liver histopathology. No significant changes in liver weight or biochemistry were observed, and no histochemical or ultrastructural changes were observed. The NOAEL was not reported by study authors, but can be considered as 850 mg/kg bw/day.	Only 6 animals/group were used in this study, and this study only included male animals. Only one dose level of phthalic acid was used. DEHP was administered via gavage, but it was not specified if phthalic acid was also administered via gavage. The vehicle used for phthalic acid was not specified; the vehicle used for DEHP and the negative control was corn oil. No other endpoints were evaluated in this study.	Hepatic/Liver: Medium	Lake et al. 1975 699519

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Phthalic anhydride - Short-term (>1-30 days)

Guideline and Animal Species, Strain, Sex	Exposure Route and Exposure Duration	Study-wide POD and Dose/ Concentration(s)	Summary	Major Limitations	Principal Target Organs/Systems and OQD*	Citation and HERO ID
No guidelines or adherence to GLP were reported. Rat; Wistar - [rat]; Male	Oral: Diet 7 days Animals were fed diet containing 2% of phthalic acid mixed in ground rat chow for 1 week (equivalent to 0 or 2,000 mg/kg-day)	**POD: 2,000 mg/kg-day (NOAEL, other)** 0, 2000 mg/kg-bw/day	Young male Wistar rats were fed control diet (N = 20 rats) or diet containing 2 percent o-phthalic acid for one week (N = 10 rats) (received dose equivalent to approximately 2,000 mg/kg-day). Treatment with o-phthalic acid did not affect body weight gain or absolute or relative weight of the testes, liver, or kidneys. Testosterone and dihydrotestosterone levels in serum and testosterone levels in testis were not significantly different compared to control animals. Treatment with o-phthalic acid did not significantly alter zinc levels in the testes, liver, or serum; however, zinc levels in the kidneys were significantly increased by 11 percent compared to control animals. No other outcomes were evaluated as part of this study. Overall, this study supports a NOAEL of 2,000 mg/kg-day o-phthalic acid with no LOAEL identified.	Only 10 animals/group were used in this study, and this study only included male animals. Only one dose level of phthalic acid was used. This study did not evaluate histopathology, clinical chemistry, nor hematology.	zinc levels in kidney: Medium	Oishi and Hiraga 1980 61572
None reported. Guinea pig; Hartley - [guinea pig]; Female	Inhalation: Aerosol 6 days Two concentrations were studied and reported as ranges. One concentration was reported as 0.05 to 0.2 mg/m3 and the other as 0.6 to 6 mg/m3. The concentration was reported as range due to the day-to-day difficulty in controlling the dust levels in the chamber.Sensitization: Animals were exposed 3 hours/day for 5 consecutive days.Challenge: Two weeks after last exposure, animals were challenged with an aerosolized phthalic anhydride-GPSA conjugate for 30 minutes.	**POD: Positive for respiratory sensitization** 0, 0.05, 0.6 mg/m^3	See footnotes for full summary [10]	Exposure details were cited in another study. It is unclear whether animals were properly acclimated in this study, or whether the air-flow rate (not reported) was appropriate. Lack of consistency is a serious concern.The study authors report the concentrations delivered as ranges (0.05 to 0.2 mg/m3 and 0.6 to 6 mg/m3) due to the day-to-day difficulty in controlling the dust levels. Atmospheres were between 65% to 80% respirable, and MMAD ranged from 5.8 to 9.8 um. Other important details (e.g., test substance purity, GSD, animal husbandry, etc.,) were missing from the report.	Sensitization: Medium	Sarlo and Clark 1992 65818

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Phthalic anhydride - Short-term (>1-30 days)

Guideline and Animal Species, Strain, Sex	Exposure Route and Exposure Duration	Study-wide POD and Dose/ Concentration(s)	Summary	Major Limitations	Principal Target Organs/Systems and OQD*	Citation and HERO ID
None reported. Guinea pig; Hartley - [guinea pig]; Female	subcutaneous 8 days Animals were injected subcutaneously with phthalate anhydride in olive oil 2 times/week for 4 weeks. After one week of rest, animals were reinjected once with the respective dose of PA. Animals were allowed to rest for another week and then tested for immune reactivity.	**POD: Positive for sensitization at 0.00067 M** 0, 0.000067, 0.00067, 0.0067Molar	See footnotes for full summary [11]	Route/method of challenge exposure (intratracheal)	Sensitization: Medium	Sarlo and Clark 1992 65818
No guideline or adherence to GLP was specified Guinea pig; Hartley - [guinea pig]; Female	Inhalation: Particulate 3 hours/day 5 days Animals were exposed for 3hrs/day for 5 consecutive days for initial exposures. After two weeks, the animals were exposed once for 30 minutes as a challenge.	**POD: Positive for respiratory sensitization** 0, 0.52, 1.21, 5.02 mg/m^3	See footnotes for full summary [12]	The study was unable to include a GPSA-only challenge control. There was a range (18-24 hrs prior to challenge during which sera was collected, which could lead to some confounding across groups.	Lung/Respiratory, Sensitization: Medium	Sarlo et al. 1994 62970
"The animal protocols used in this study were reviewed and approved for ethical and scientific care procedures by the Pusan National University-Institutional Animal Care and Use Committee (PNU-IACUC; Approval Number PNU-2013-0410)." Mouse; IL-4/Luc/CNS-1 Tg mice; Unknown	Dermal 3 days/week 2 weeks	**POD: 1,125 mg/kg/day** 0, 15%	See footnotes for full summary [13]	A major limitation and reporting deficiency is that the authors do not report the results for vehicle controls for this endpoint, precluding the ability to interpret the effect of phthalic anhydride on IL-4 from these data. Other limitations include a small sample size, failure to report the sex of the animals, and the inclusion of only one dose in the study design.	Immune/Hematological: Medium	Sung et al. 2016 5179546

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Phthalic anhydride - Short-term (>1-30 days)

Guideline and Animal Species, Strain, Sex	Exposure Route and Exposure Duration	Study-wide POD and Dose/ Concentration(s)	Summary	Major Limitations	Principal Target Organs/Systems and OQD*	Citation and HERO ID
Specific guideline was not reported, but study was a modified version of OECD 429. Study did not report if GLP conditions were adhered to. Mouse; Balb/c - [mouse]; Both	Dermal 3 days Test substance was applied to the dorsum of both ears for 3 consecutive days.	**POD: Positive for skin sensitization (25% w/v)** 0, 25%	See footnotes for full summary [14]	Husbandry conditions were not reported. Some significant findings were only reported in text; data were not shown. Animal weights were not reported.	Sensitization: High	Vandebriel et al. 2000 5160984

* Overall Quality Determination

[1] 5160442: Groups of rats (20/group; sex and strain not specified) were exposed via inhalation to 0 or 500 ug of phthalic anhydride/cm3 of air for 6 hours/day for 5 consecutive days. The methods of exposure were not described and the accuracy of the exposure concentrations is questionable. Following a three-week resting period, the exposed animals were challenged with a single 6-hour exposure to 500 ug of phthalic anhydride/cm3 (+/+ group); control animals were left unchallenged (-/- group). Details of the control group (air-only or untreated) were not provided. Animals were sacrificed following the rest period or challenge exposures and lungs were removed for gross examinations and the number of hemorrhagic foci per lung was recorded. Lung weights and volumes were measured. No other endpoints were reported. Results showed that +/+ animals had a mean of 15 hemorrhagic foci/lung vs. a mean of 2 for the -/- group. More than 50% of the exposed rats had more than 10 foci per lung vs. 0% for the controls. No differences in relative lung weights or relative lung volumes were observed (data not shown). Phthalic anhydride was considered to be a respiratory sensitizer. 500 ug/cm3 is equivalent to 500,000 mg/m3.** The study included a second experiment in which two groups (20/group) were similarly exposed to 500 ug of phthalic anhydride/cm3 of air for 6 hours/day for 5 consecutive days. After the three-week rest period, one group was challenged with 500 ug trimellitic anhydride (TMA)/ cm3 air and the other group was left unchallenged (+/- group). The mean number of foci per lung to be 4 and 10, respectively, and the % of rats with more than 10 foci per lung to be 8% and 42%, respectively for the +/- and +/+ groups. No differences in relative lung weights or relative lung volumes were observed (data not shown).***Additional information available in the associated reference (HEROID 12980190) provides additional information such as this study stating "No microscopic lesions were observed in the lungs from the three select control rats." In this study, 10 male and female sprague dawley rats were exposed to aerosolized phthalic anhydride (500 ug/m3 was target concentration) for 6 hours/day for 5 consecutive days and another set of 10 rats per gender was used for the control groups. 3 weeks later, the phthalic anhydride treated groups received another dose at the same concentration for 6 hours. There were "means of 20 and 11 external hemorrhagic foci in the lungs" of male and female rats, respectively. In the treated groups, select rats displayed "statistically significant" increases in the phthalic anhydride specific IgG serum antibodies, and mild parabronchial hyperplasia, lymphoid hyperplasia, alveolar hemorrhages and perivascular acute and chronic inflammation in 1/3, 2/3, and 1/3 of the rats, respectively.

[2] 1222879: The purpose of this study was to develop a respiratory LLNA protocol and specifically, to determine whether inhalation allergens could induce proliferation in lymph nodes, and to test if the potency of responses is comparable between dermal and inhalation routes. Several known respiratory allergens, including phthalic anhydride, and contact allergens were used. The developed protocol is similar to the existing skin LLNA protocol, but with an inhalation induction and examination of both draining and local lymph nodes. Groups of male BALB/c mice (6/group) were exposed, nose-only, to an aerosolized phthalic anhydride (purity ≥99%), with a mean analytical aerosol concentration of 14.2 mg/m3 for 45, 90, 180, or 360 min/day for three consecutive days. A separate group of test animals (12/group) were exposed by inhalation to the aerosolized acetone vehicle for 360 min/day for 3 days, as a negative control. Test aerosols were generated from solutions of the test substance in acetone; aerosolized acetone evaporated before reaching the animal's nose, and the final concentration was <600 ppm, which is non-irritating. An MAMD of 2.6 μm and a GSD of 4.4 were reported. Animals were necropsied 3 days after the last exposure on day 5. For comparison, mice (3/group) were exposed dermally in a traditional LLNA assay. Animals in the modified (inhalation) assay are reviewed here; dermally exposed animals are reviewed separately (different form), although some results are reported here for comparison. All animals were observed at least once daily for mortality and signs of toxicity and weighed shortly before the first treatment and just prior to necropsy. Several draining mandibular lymph nodes were excised at necropsy, lymph node cells were harvested, and proliferation was assessed ex vivo using [3H]thymidine labeling. To assess the ability to distinguish between respiratory and contact sensitizers, cytokine production was assessed in isolated draining and local lymph node cells after cultivation with concanavalin A (5 ug/mL) for 24 hrs. (results reported in HERO 652441). The lungs, with the trachea and larynx, were weighed. All animals were examined for gross abnormalities at necropsy (organs not specified). The respiratory tract was also examined histologically in controls and animals exposed for 360 min/day only. No mortality of test animals was reported. Clinical signs noted during inhalation exposure were piloerection and hunched posture, blepharospasm, dyspnea, and sluggishness (incidences not reported). Slight to moderate losses in body weight between day 0 and day 5 were observed following 90, 180, or 360 min/day exposure to phthalic anhydride (data not reported). The mandibular lymph nodes draining the nasal tissues were enlarged and had significant increases in proliferation following exposure to phthalic anhydride. Increased relative lung weight was observed in test animals following 90, 180, or 360 min/day exposure to phthalic anhydride (data not reported). No changes were reported in absolute lung weights. Upon gross necropsy, air-filled intestines were noted in exposed test animals. Histopathological examinations showed slight to moderate inflammation and slight squamous cell metaplasia in the nasal cavities of 2/6 mice exposed for 360 min/day. Squamous cell metaplasia of the larynx was also observed in 2/6 exposed mice. Incidences in controls were not reported. No lesions were observed in the lungs. The test substance showed a positive proliferative response (i.e., SI ≥3) in mandibular lymph nodes in animals exposed for 90 minutes (SI = 3.6). SI values in other groups were 1.0 (vehicle), 2.9, 2.3, and 2.9 in the 45 min, 180 min, and 360 min/day exposure groups, respectively. No positive responses were observed in auricular lymph nodes. The test substance was positive for sensitization following dermal contact (SI = 93). Cytokine analysis showed induction of IL-4 and IL-10 in mandibular lymph nodes after inhalation exposure, in groups exposed for 45 or 90 minutes, but not in groups exposed for 180 or 360 min. These cytokines were also induced in auricular lymph nodes following dermal exposure to PA. Induction of IFN-gamma was only observed following dermal exposure, indicating it could not discriminate between respiratory and contact sensitizers. The study authors calculated an effective dose (ED3), representing stimulation rates that are 3-fold of control values in relation to the respiratory exposure dose) of 63 µg.The test substance, a known respiratory sensitizer, was positive for sensitization in the respiratory LLNA protocol tested.

[3] 5177984: In a primarily mechanistic study, focused on clarifying "the role of GATA3 in the pathogenesis of allergic skin diseases", wild type mice (strain, sex not specified; n=6-8/group) and transgenic mice overexpressing human GATA3 on a C57BL/6 and DBA/2 background (sex not reported; n=6-8/group) had 50 ul of acetone-olive oil (control) or 1%, 5% or 10 % phthalic anhydride solution (4:1 v/v acetone-olive oil) applied to the dorsum of the ear 3 times a week for 3 weeks. Ear thickness was measured on days 0, 7, 12, 16, and 18. Additional endpoints evaluated included ear histopathology (examinations for the presence of edema and accumulation of inflammatory cells); serum IgE, G1, G2a and G3; cytokine and chemokine levels in lysate from ear and thymus (mouse cytokine array assay); and myeloperoxidase (MPO) activity in ear skin homogenate. Except for cytokine and chemokine analysis, the study did not report results of statistical analysis between treated animals and controls; only results for statistical analysis between Tg and WT animals were provided. Sample sizes were not provided, precluding the ability to independently analyze the data. In WT mice (this form), ear thickness increased in a time and dose-related manner in PA-treated mice, with no notable increase in controls (statistical analysis was not conducted). The absolute weight of the auricular lymph nodes visually increased in a dose-related manner relative to controls. No histological changes were observed in the control group, whereas mice exposed to 5% PA showed increasing levels of edema, epidermal hyperplasia and infiltration of mast cells (findings for other dose groups not reported). Serum levels of IgE were visibly elevated in all treatment groups, increasing in a dose-related manner, and IgG1 levels were visibly elevated, compared to controls, in the 5% and 10% treatment groups. No changes in serum IgG2 or IgG3 (Th1-type Igs) were seen, compared with controls. In the thymus, statistically significant decreases in IFN-γ and increases in IL-4 were seen in WT animals treated with PA, compared with controls; however, the dose group was not reported. In the ear, RANTES, IL-6, VEGF and M-CSF were significantly increased in PA-treated animals, compared with controls, but again, the dose group was not specified. MPO activity was low/not observed in controls or in the 1% PA groups; activity was visually increased in the 5% and 10% PA treatment groups.In transgenic mice (separate form), ear thickness increased in a time and dose-related manner in treated mice, again with no notable increase in the controls. Ear thickness increased at a faster rate in Tg mice, compared with WT mice, and was statistically significantly thicker than WT in all dose groups. The absolute weights of auricular lymph nodes were visually increased in a dose-related manner, compared with controls. Within groups (including controls and all treatment groups), LN weights were significantly greater in the Tg animals than in WT animals. No histological changes were observed in the control group, whereas Tg mice exposed to 5% PA showed increasing levels of edema, epidermal hyperplasia and infiltration of mast cells (findings for other dose groups not reported). Compared to WT animals, the thickness of the epidermal layer and mast cell infiltration into the dermis were significantly greater in Tg animals. Serum levels of IgE were visibly elevated in all treatment groups, increasing in a dose-related manner, and IgG1 levels were visibly elevated, compared to controls. Serum IgG2 or IgG3 levels appeared to be comparable to controls. In the thymus, statistically significant decreases in IFN-γ and increases in IL-4 were seen in WT animals treated with PA, compared with controls; however, the dose group was not reported. In the ear, RANTES, IL-6, VEGF and M-CSF were significantly increased in PA-treated animals, compared with controls, but again, the dose group was not specified. In both cases, these changes were significantly greater in transgenic mice compared with the WT mice. MPO activity was low/not observed in controls or in the 1% PA groups; activity was visually increased in the 5% and 10% PA treatment groups, and the increases in Tg mice were significantly greater than those in the WT mice. Western blots showed that PA treatment in transgenic mice significantly increased the relative expression of GATA3, compared with controls. Due to the lack of statistical analysis in WT animals between the PA-treated groups and the controls, reliable toxity values cannot be determined. The test substance was positive for inducing an allergic skin response.

[4] 5177984: In a primarily mechanistic study, focused on clarifying "the role of GATA3 in the pathogenesis of allergic skin diseases", wild type mice (strain, sex not specified; n=6-8/group) and transgenic mice overexpressing human GATA3 on a C57BL/6 and DBA/2 background (sex not reported; n=6-8/group) had 50 ul of acetone-olive oil (control) or 1%, 5% or 10 % phthalic anhydride solution (4:1 v/v acetone-olive oil) applied to the dorsum of the ear 3 times a week for 3 weeks. Ear thickness was measured on days 0, 7, 12, 16, and 18. Additional endpoints evaluated included ear histopathology (examinations for the presence of edema and accumulation of inflammatory cells); serum IgE, G1, G2a and G3; cytokine and chemokine levels in lysate from ear and thymus (mouse cytokine array assay); and myeloperoxidase (MPO) activity in ear skin homogenate. Except for cytokine and chemokine analysis, the study did not report results of statistical analysis between treated animals and controls; only results for statistical analysis between Tg and WT animals were provided. Sample sizes were not provided, precluding the ability to independently analyze the data. In WT mice (other form), ear thickness increased in a time and dose-related manner in PA-treated mice, with no notable increase in controls (statistical analysis was not conducted). The absolute weight of the auricular lymph nodes visually increased in a dose-related manner relative to controls. No histological changes were observed in the control group, whereas mice exposed to 5% PA showed increasing levels of edema, epidermal hyperplasia and infiltration of mast cells (findings for other dose groups not reported). Serum levels of IgE were visibly elevated in all treatment groups, increasing in a dose-related manner, and IgG1 levels were visibly elevated, compared to controls, in the 5% and 10% treatment groups. No changes in serum IgG2 or IgG3 (Th1-type Igs) were seen, compared with controls. In the thymus, statistically significant decreases in IFN-γ and increases in IL-4 were seen in WT animals treated with PA, compared with controls; however, the dose group was not reported. In the ear, RANTES, IL-6,

VEGF and M-CSF were significantly increased in PA-treated animals, compared with controls, but again, the dose group was not specified. MPO activity was low/not observed in controls or in the 1% PA groups; activity was visually increased in the 5% and 10% PA treatment groups.In transgenic mice (this form), ear thickness increased in a time and dose-related manner in treated mice, again with no notable increase in the controls. Ear thickness increased at a faster rate in Tg mice, compared with WT mice, and was statistically significantly thicker than WT in all dose groups. The absolute weights of auricular lymph nodes were visually increased in a dose-related manner, compared with controls. Within groups (including controls and all treatment groups), LN weights were significantly greater in the Tg animals than in WT animals. No histological changes were observed in the control group, whereas Tg mice exposed to 5% PA showed increasing levels of edema, epidermal hyperplasia and infiltration of mast cells (findings for other dose groups not reported). Compared to WT animals, the thickness of the epidermal layer and mast cell infiltration into the dermis were significantly greater in Tg animals. Serum levels of IgE were visibly elevated in all treatment groups, increasing in a dose-related manner, and IgG1 levels were visibly elevated, compared to controls. Serum IgG2 or IgG3 levels appeared to be comparable to controls. In the thymus, statistically significant decreases in IFN-γ and increases in IL-4 were seen in WT animals treated with PA, compared with controls; however, the dose group was not reported. In the ear, RANTES, IL-6, VEGF and M-CSF were significantly increased in PA-treated animals, compared with controls, but again, the dose group was not specified. In both cases, these changes were significantly greater in transgenic mice compared with the WT mice. MPO activity was low/not observed in controls or in the 1% PA groups; activity was visually increased in the 5% and 10% PA treatment groups, and the increases in Tg mice were significantly greater than those in the WT mice. Western blots showed that PA treatment in transgenic mice significantly increased the relative expression of GATA3, compared with controls. Due to the lack of statistical analysis in transgenic animals between the PA-treated groups and the controls, reliable toxity values cannot be determined, although responses were visible in all treatment groups. The test substance was positive for inducing an allergic skin response.

[5] 83939: Dose calculations: The density of phthalic anhydride is 1.53 g/ml. 50 ul of a 12% solution was applied to the mice. The following calculations were performed: 1.53 g/ml * 0.05 ml = 0.0765 g or 76.5 mg. 12% of 76.5 mg is 9.18 mg. The default body weight of BAF1 hybrid mouse (EPA 1988) for subchronic treatment is 0.0204 kg, therefore 9.18 mg/0.0204 kg= 450 mg/kgFemale BALB/c mice (12/group) received a dermal application of 50ul a 12% phthalic anhydride in vehicle (4:1 acetone olive oil, v/v) on their shaved flanks (day 0) (450mg/kg). Thirty minutes prior and 30 minutes after application, and from day 1-4 mice received a 200 ul injection of saline (control for another experiment studying antagonists). Control mice underwent dermal application of the vehicle and saline injections. On day 7, (6 mice/group) were sacrificed and blood was collected for serum total IgE and IgG2a assessment. Spleen cells were cultured with ConA and cytokine levels (IL-2, IL-4, IL-10 and INF-g) in supernatant were determined. The remaining mice (6/group) were challenged by the application of vehicle or 6.25% phthalic anhydride (234 mg/kg) on the the dorsum of both ears. Mice were sacrificed on day 11 and blood was collected for serum total IgE and IgG2a assessment. Each experiment was performed 3 times. In mice sacrificed on day 7, serum levels of total IgE were significantly increased compared to control in 2 of the 3 experiments. No change in IgG2a levels were seen. In cultured splenocytes from treated mice, significant increases in IL-4 were seen in 3 of the 3 experiments and IL-10 in 2 or the 3 experiments compared to control. In mice sacrificed on day 11, serum levels of total IgE were significantly increased compared to control in 3 of the 3 experiments. No change in IgG2a levels were seen.

[6] 5177112: 3-day induction tests.In the main test, Hartley Crl: (HA) BR, (COBS-VAF2) guinea pigs (10/sex/treatment group or 5/sex/group for controls) were dermally exposed to 0 or 20% phthalic anhydride, in an acetone vehicle, via a dermal adhesive patch on the left flank, for 6 hours on days 3, 10 and 17 of an induction phase. Vehicle control group animals were additionally exposed on days 1, 5, 8, 12, 15, 16, and 17 (a total of 9 exposures); these animals also served as controls for a 9-day induction experiment (reported separately). Animals were monitored for mortality and clinical signs for the duration of the study, and body weights were measured at the beginning and end of the study and on day 31. During the challenge phase, the left flank was exposed to acetone vehicle, while the right flank was exposed to 20% phthalic acid for 6 hours on day 29. Skin reactions were scored for erythema and edema (on a 0-3 intensity scale) at 24, 48 and 72 hours after the challenge exposure. A reaction was considered positive if the reaction persisted for 48 hours at a score $\geq$1 or was a greater score than that of the control group.No animals died during the study. No test substance-related clinical signs were observed. No differences in body weight gains were observed (data not shown). After the challenge phase, 85% of reactions were considered positive (10/10 males and 7/10 females had positive reactions). In the control group, 20% of reactions were considered positive (2/5 males and 0/5 females). The positive responses in some control animals could suggest an irritation effect of the test substance; however, the study authors noted that the higher incidence of positive reactions is suggestive of a sensitzation response.Phthalic anhydride was considered positive for skin sensitisation.Screening Test: Hartley Crl: (HA) BR, (COBS-VAF2) guinea pigs (5/males/group) were exposed to 0 or 20% phthalic anhydride in acetone vehicle via dermal adhesive patch exposure on the left flank for 6 hours on days 3, 10 and 17 of the induction phase. The control group was additionally exposed on days 1, 5, 8, 12, 15, 16, and 17 (a total of 9 exposures; animals also served as the control for the 9-day induction experiment). Animals were monitored for mortality and clinical signs for the duration of the study, and body weights were measured at the beginning and end of the study and on day 31. During the challenge phase, the left flank was exposed to acetone vehicle, while the right flank was exposed to 20% phthalic anhydride for 6 hours on day 29. Skin reactions were scored for erythema and edema (on a 0-3 intensity scale) at 24, 48 and 72 hours after the challenge exposure. A reaction was considered positive if the reaction persisted for 48 hours at a score $\geq$1 or were a greater score than that of the control group. Animals were challenged a second time on day 43 under the same experimental conditions described on day 29. No animals died during the study. No clinical signs of toxicity were observed. No differences in body weight gains were observed (data not shown). After the first challenge phase, 1/5 animals had positive reactions; after the second challenge phase 1/5 animals had a positive reaction. In the control group, 0/5 animals had positive reactions after the first challenge, and 1/5 after the second challenge.

[7] 5177112: 9-day induction tests.In the main test, Hartley Crl: (HA) BR, (COBS-VAF2) guinea pigs (10/sex/group or 5/sex/group for controls) were exposed to phthalic anhydride in an acetone vehicle, via a dermal adhesive patch exposure on the left flank, for 6 hours/day. Exposures varied with concentration on different days of the induction phase and consisted of 20% phthalic anhydride on days 1, 3, 5, and 8, and 10% phthalic anhydride on days 10, 12, 15, 16 and 17. Animals were monitored for mortality and clinical signs for the duration of the study, and body weights were measured at the beginning and end of the study and on day 31. During the challenge phase, the left flank was exposed to acetone vehicle, while the right flank was exposed to 20% phthalic anhydride for 6 hours on day 29. Skin reactions were scored for erythema and edema (on a 0-3 intensity scale) at 24, 48 and 72 hours after the challenge exposure. A reaction was considered positive if the reaction persisted for 48 hours at a score $\geq$1 or were a greater score than that of the control group.No animals died during the study. No test substance-related clinical signs were observed. No difference in body weight gains were observed (data not shown). After the challenge phase, 65% of reactions were considered positive (10/10 males and 3/10 females had positive reactions). In the control group, 20% of reactions were considered positive (2/5 males and 0/5 females). The positive responses in some control animals could suggest an irritation effect of the test substance; however, the study authors noted that the higher incidence of positive reactions is suggestive of a sensitzation response.Phthalic anhydride was considered positive for skin sensitization.Screening Test:Hartley Crl: (HA) BR, (COBS-VAF2) guinea pigs (5/males/group) were exposed to 0 or 20% phthalic anhydride in acetone vehicle via dermal adhesive patch exposure on the left flank for 6 hours/day, 3 times/week for 3 weeks (9 applications in total). Animals were monitored for mortality and clinical signs for the duration of the study, and body weights were measured at the beginning and end of the study and on day 31. During the challenge phase, the left flank was exposed to acetone vehicle, while the right flank was exposed to 20% phthalic anhydride for 6 hours on day 29. Skin reactions were scored for erythema and edema (on a 0-3 intensity scale) at 24, 48 and 72 hours after the challenge exposure. A reaction was considered positive if the reaction persisted for 48 hours at a score $\geq$1 or was a greater score than that of the control group.No animals died during the study. No clinical signs of toxicity were observed. No difference in body weight gains was observed (data not shown). After the first challenge phase, 2/5 animals had positive reactions; after the second challenge phase, 2/5 animals had positive reactions. In the control group, 0/5 animals had positive reactions after the first challenge, and 1/5 after the second challenge.

[8] 1940789: The respiratory sensitization potential of PA was evaluated in Balb/C mice (6 females/group). Groups consisted of−/− (sensitization and challenge with solvent only), +/− (sensitization with test solution and challenge with solvent only) and +/+ (sensitization and challenge with test solution). For sensitization, a 25uL volume of the test solution (0.3% PA in 4:1 acetone:olive oil) or solvent alone was applied to the dorsum of

both ears on days 1-3, 8-10, and 15-17 (9 applications total). After a two-week rest period, animals were challenged intratracheally with 50ul of 0.03% PA in acetone (diluted with PBS), or solvent alone. Animals were sacrificed one day after challenge. Blood samples collected for measurements of total IgE and IgG1. Lung lymph nodes were collected for number of total and B cell counts, ex situ cytokine production, and gene expression of GATA-3, STAT6, and CCR4. BALF fluids were examined for number of cells, differential cell counts, total IgE and IgG1, chemokines (MCP-1, MIP1-α, MIP1-β, and EOTAXIN-1) and cytokines (IL-6 and TNF-α), and gene expression of CCR3. In Serum and BALF, PA +/+ treatment groups showed a statistically significant increase in total IgE and IgG1 compared with the -/- control group. BALF total cell counts, as well as eosinophil and neutrophil counts, were significantly increased in the +/+ group, compared with both -/- and +/- groups. Lymph node analysis also showed significant increases in total cells, IgE positive B cells and in MCH II positive B cells in the +/+ group (relative to results in both -/- and +/- groups).Other mechanistic results included: significantly elevated cytokines (IL-6, TNF-α, MCP-1, M1P1-β, and EOTXIN-1; levels of M1P1-α were unchanged) and an approximate >10 fold increase in CCR3 gene expression in BALF from +/+ mice relative to both -/- and +/- groups. Significant increases in IL-4, IL-5, IL-13, and INF-γ, but no changes in gene expression of Stat6, GATA-3 or CCR4 in lung-associated lymph node supernatants from +/+ mice, compared to the other groups. Phthalic anhydride was considered positive for induction of immediate-type respiratory reactions in mice following a single intratracheal challenge. Using a density of 1.53 g/cm3 for phthalic anhydride, and a default mouse body weight of 0.02kg, approximate doses were calculated using the following formulae: (Density x volume applied x percentage applied))/ BWApplication of 25ul of 0.3% PA is equivalent to approximately 574 mg/kg per applicationInjection of 50ul of 0.03% PA is equivalent to a dose of approximately 114.75 mg/kg** In addition to PA, the study also evaluated trimellitic anhydride (TMA) and toluene diisocyanate (TDI), which are also known respiratory allergens; 2,3-D-butyl (DB), a chemical of unknown allergenicity; 2,4-dinitrochlorobenzene (DNCB), a confirmed contact allergen, and sodium dodecyl sulfate (SDS), a known irritant.

[9] 12980190: In a respiratory sensitization study, Sprague-Dawley rats (10/sex/group) were either untreated or exposed to 525 µg/m3 phthalic anhydride (PA) as an aerosol via whole-body inhalation 6 hours/day for 5 days. Animals were allowed to rest for 3 weeks, and the PA-exposed rats were challenged with 481 µg/m3 PA for 6 hours. Controls rats were not sham (air-exposed) and were left untreated. The study did not include an unsensitized but challenged control group. Approximately eighteen hours following the challenge exposure, all animals were sacrificed. Endpoints evaluated included mortality, body weight (weekly), serum IgG, gross necropsy of the lungs, lung weight, lung volume, and histopathology of the lungs of 2/males/group and 1 female/group.All animals survived until the end of the study. Terminal body weights were reported; however, the study authors indicated that exposed rats were fasted during the exposure periods, whereas controls were unfasted. Therefore, the controls were not a valid comparator for this endpoint. Serum IgG levels in the rats sensitized and then challenged with PA were significantly increased in males (149-fold) and females (34-fold) compared to the respective untreated controls. No significant difference in absolute or relative lung weights, or lung volumes were seen. The means of lung foci/lung were significantly increased in both males (5-fold) and females (5.5-fold) compared to their respective controls. Seven males and 3 females in the PA-exposed groups had ≥10 foci/lung, which was defined as a positive response; none of the control animals had this response. Histological changes observed in the PA-exposed lungs were mild parabronchial lymphoid hyperplasia (1/3), alveolar hemorrhage (2/3), and perivascular acute and chronic inflammation (1/3). No microscopic lesions were seen in the controls. A second experiment was conducted to test for cross-reaction with trimellitic anhydride. This experiment is not further described here or included in this assessment. Although the study authors conclude phthalic anhydride induces respiratory sensitization in rats; the lack of appropriate controls cannot rule out the possibility that effects were due to inhalation of particulates in general, rather than to the test substance.

[10] 65818: In a respiratory sensitization study, female Hartly smooth-haired guinea pigs were exposed to concentrations of phthalic anhydride (PA) dust ranging from 0.05 to 0.2 mg/m3 (n=5) or 0.6 to 6 mg/m3 (n=6) 3 hours/day for 5 consecutive days. Study authors state that concentrations were "reported as ranges due to the day-day difficulty in controlling the dust levels in the chamber ". The PA dust was reported to be between 65-80% respirable (<10um) with a mean mass diameter between 5.8 to 9.8 µm. An air control group (n=8) was also included. Two weeks after the final exposure, all animals were challenged for 30 minutes with an aerosolized phthalic anhydride-guinea pig serum albumin (GPSA) conjugate (25:1; 95% respirable). Sera was collected from animals before the initial chemical exposure (served as baseline) and 24 hours prior to the respiratory challenge. Levels of sera IgG antibodies specific for PA-GPSA or to GPSA alone were determined by ELISA.Respiratory rate and breath peak height were monitored during the initial exposure, 30 minutes prior to the challenge exposure, and during the challenge exposure. Significant respiratory reaction was defined as an increase in respiratory rate > 46% and/or an increase in breath peak height >50%. Passive cutaneous anaphylaxis (PCA) testing was performed to determine IgG1a antibody titers. Naïve guinea pigs were intradermally injected with 100 μL of sera from control and exposed animals diluted 1/5 to 1/2560 in saline. Baseline sera served as each animal's own control. Four hours later, anesthetized animals were intracardially injected with 1.0 ml of 500 ug/ml antigen (PA-GPSA or GPSA) in a 1% Evans blue dye isotone solution. IgG1a titers were determined 30 minutes following intracardial injection.When challenged with the PA-GPSA conjugate, immediate-onset respiratory reactions were seen in 6/6 guinea pigs sensitized with the higher concentration (0.6 to 6 mg/m3); no guinea pigs initially exposed to the lower concentration range (0.05 to 0.2 mg/m3) had significant respiratory reactions. Affected animals experienced "transient increases in respiratory rates always followed by sustained increases in peak height which were evident during and up to 15 minutes after conjugate challenge". Increased sera IgG and IgG1a antibodies to PA-GSPA were seen in the higher concentration group. No detectable levels of antibodies were seen in the lower concentration group (data not shown).Phthalic anhydride was positive for respiratory sensitization at 0.6 to 6 mg/m3.

[11] 65818: Female Hartly smooth-haired guinea pigs (10/group) were subcutaneously injected with 400 μL of 0 (vehicle), 6.7 10^-5 M, 6.7 10^-4 M, or 6.7 10^-3 M phthalate anhydride (PA) in olive oil 2 times/week for 4 consecutive weeks. An additional control group was injected with 6.7 x 10^-4 phthalic acid. After a 1-week rest period, animals were reinjected with 400 μL of either control or PA at the respective doses. Animals were allowed to rest for an additional week before being evaluated for immune reactivity via three separate tests: a passive cutaneous anaphylaxis (PCA) test, and intratracheal challenge, and an active cutaneous anaphylaxis (ACA) skin test. In the respiratory reactivity test, 100uL of a PA-guinea pig serum albumin (GPSA) conjugate (500 ug/ml of conjugate based on protein) was delivered to the tracheal bifurcation. Changes in breathing pattern were monitored visually for 10 minutes following the challenge. "A significant respiratory reaction was defined as diaphragmatic contractions occurring at a minimum of every 36 to 40 normal breaths occurring over an observation period of 10 min." For ACA skin test: Forty-eight hours after guinea pigs were intratracheally challenged, the same guinea pigs were anesthetized and intracardially injected with 1 mL of 0.1% Evans blue dye in saline. Thirty minutes later, these animals were intradermally injected with 50 uL of 0.04, 0.4, 4, 40, or 400 ug/mL of PA-GPSA or GPSA alone. It was not specified how many animals were injected with each concentration, or if all animals were injected with all concentrations at different sites. Visible bluing at the antigen injection site was considered a positive response (identification of IgG1a and/or IgE). Passive cutaneous anaphylaxis (PCA) testing was performed to determine IgG1a antibody titers. Naïve guinea pigs were intradermally injected with 100-ul of sera (collected at day 1 following end of the initial exposure period) diluted 1/5 to 1/2560 in saline. Four hours later, anesthetized animals were intracardially injected with 1.0 ml of 500 ug/ml antigen (PA-GPSA or GPSA) in a 1% Evans blue dye isotone solution. Sera IgG1a titers were determined 30 minutes following intracardial injection. Positive respiratory reactivity responses were seen after intratracheal challenge in 8/10, 9/10 and 6/10 animals in the low- mid-, and high-dose groups respectively. Control animals and those receiving phthalic acid did not have an increased respiratory response. Positive skin reactivity in the ACA test (visible bluing at the antigen injection site) was seen in 10/10, 10/10 and 8/10 animals in the low-, mid-, and high-dose groups, respectively. No skin reaction was seen in the control (animals injected with vehicle but challenged with PA-GPSA) or in animals injected with phthalic acid. Skin tests were also negative to unmodified GPSA (data not shown).Serum titers of IgG increased in a dose-related manner following injections. Serum allergic (IgG1a) titers were increased in all dose groups, but the highest response was seen in the mid-dose group following the PCA test. Antibody titers were not seen in the vehicle control or in the phthalic acid control group.Phthalic anhydride was positive for sensitization at 6.7 x10-5 M.

[12] 62970: In a respiratory sensitizations study, female Hartley smooth-haired guinea pigs (8/low and mid exposure groups and 16/control and high exposure groups) were exposed, whole body, to phthalic anhydride (PA) dust at targeted levels of 0, 0.5, 1.0, or 5.0 mg/m3 3 hrs/day, for 5 consecutive days. The analytical TWA concentrations were 0, 0.52, 1.21, and 5.02 mg/m3 with corresponding MMADs of 3.12, 3.26, and 3.91, respectively. The % respirable (≥10 um) ranged from 90-95.2%. Prior to exposure PA dust was micronized to respirable-sized particles (5 um). One day after exposure, 8 animals per group were transported to another facility (further

described below). After a two-week rest, the remaining 8 control and high-exposure animals were challenged, head-only, with 5.0 mg/m³ (5.53 mg/m³ TWA) PA-dust for 30 minutes. The bodies of the animals were placed in plethysmographs. Prior to the challenge, animals were allowed to acclimate for 30 minutes and respiratory rates were recorded, establishing a baseline. Respiratory rates were then measured during the 30-minute exposure period and for up to 60 minutes post-exposure. Percent changes in pressure and respiratory rates were calculated from the baseline. Similarly, the other 8 animals/group in facility #2 were challenged using the same methods, but with 2.0 mg/m3 aerosolized PA-GPSA conjugate. Control groups in the study included an air-exposed/PA-dust challenge, an air-exposed PA-GPSA challenge and air-exposed/air-challenge animals. A GPSA aerosol control was not included due to a technical issue. Sera was collected from all animals before the first exposure (baseline) and then 18-24 hours before respiratory challenge to measure IgG antibodies to PA-GPSA or to GPSA alone. All animals were sacrificed 24 hours after the challenge. Each animal was grossly examined. Lungs were removed for histopathological examination. The study also conducted passive cutaneous anaphylaxis (PCA) testing. Briefly, naive guinea pigs were intradermally injected with 100 ul of sera (diluted 1:4 to 1:132 in saline) collected from air-control and PA-exposed animals. Four hours or 4 days later, animals were intracardially injected with 1.0 mL of 500 μg/mL PA-GPSA or GPSA in isotonic solution. IgG1a and IgE antibody titers were measured 4 hrs or 4 days later, respectively. Heat-treated sera were included as a control in the 4-day PCA test.In animals exposed to 5.02 mg/m3 PA-dust and challenged with 5.53 mg/m3 PA-dust, there were no significant changes to respiratory rates, compared with air-exposed/PA-dust challenged animals. In animals exposed to 0.52, 1.21, or 5.02 mg/m3 and challenged with 2.0 mg/m3 aerosolized PA-GPSA conjugate, significant increases in respiratory rates were observed in 1/8, 0/8, and 4/8 animals in the 0.52, 1.21and 5.02 mg/m3 exposure groups, respectively. A significant change in pressure was observed in 1/8, 1/8 and 3/8 animals from the same groups. Levels of sera IgG antibodies significantly increased with increasing initial exposure levels. Histopathology showed hemorrhagic foci in the lungs of 8/8 animals exposed and challenged with 5.0 mg/m3 PA-dust, and 3/8 animals had >189 foci. Minimal type II hyperplasia was also observed. In controls (animals exposed to air and challenged with PA-dust), 1-2 foci were observed in 5/8 of these animals. Animals with greater numbers of foci also showed higher levels of IgG antibodies. No foci were observed in animals challenged with PA-GPSA, so lungs were not examined further.Significant dose-related increases in serum IgG levels were seen in animals exposed to 0.52, 1.21, or 5.02 mg/m3 compared to air control. The PCA test showed allergic IgG1a antibodies were present in 3/8, 1/8, and 5/8 animals from the 0.52, 1.21, and 5.02 mg/m3 exposure groups, respectively. Some, but not all, animals with allergic IgG1a also showed respiratory reactivity upon conjugate challenge. None of the sera samples contained IgE. Overall, the test substance was positive for respiratory sensitization, and the authors identified 0.052 mg/m3 as being at or near the minimal concentration of PA-dust required to immunize and allergically sensitize guinea pigs.

[13] 5179546: Dose calculations: The density of phthalic anhydride is 1.53 g/ml. 100 ul of a 15% solution was applied to the mice. The following calculations were performed: 1.53 g/ml * 0.10 ml = 0.153 g or 153 mg. 15% of 153 mg is 22.95 mg. The default body weight of BAF1 hybrid mouse (EPA 1988) for subchronic treatment is 0.0204 kg, therefore 22.95 mg/0.0204 kg= 1,125 mg/kgYoung (2-month-old) and old (12-month-old) IL-4/Luc/CNS-1 Tg mice (generated by breeding male IL-4/Luc/CNS-1 Tg and female HR1 mice) were administered 100ul of 15% phthalic anhydride (1,125 mg/kg/day) dissolved in 4:1 acetone: olive oil, v/v or vehicle on the dorsum of the ears three times a week for 2 weeks (n=4-5/group; sex not reported). Body weights were measured throughout the study. After 2 weeks of treatment, ear color, vein, morphological characteristics and thickness were evaluated. Mice were injected(i.p) with D-luciferin and whole body and organ images (lung, kidney, spleen, heart, mesenteric lymph nodes, thymus and pancreas) were taken for 3 minutes. Mice were then sacrificed. Endpoints evaluated included serum IgE levels, organ weight (lung, kidney, spleen, heart, mesenteric lymph node, thymus and pancreas), histology on ear (including mast cell infiltration) and protein expression IL-6 and VEGF in ear (via Western blot). Body weights in both groups remained constant throughout the experimental period (data not shown). In treated mice, ear color changed significantly (from a fleshy tint to a dark brown), the ear vein became thickened, and ear thickness significantly increased in young (81%) and old (74%) mice compared to age-matched controls. Significant increases in spleen (82%) and mesenteric lymph node (63%) weights were seen in young mice after treatment whereas significant decreases in thymus weights were seen in young (57%) and old (50%) mice compared to control. Other organ weights were not significantly different from control. Histologically, significant increases in the thickness of the epidermis and dermis of the ear tissue were seen in treated mice compared to control; furthermore, older treated mice had significanlty thicker epidermis and dermis (120-125%) compared to younger treated mice. The number of mast cells in the dermis region was significantly increased in young and old treated mice compared to controls; older mice had significantly more mast cells (25%) than younger mice. Serum IgE levels were significantly increased in young (1100%) and old (85%) mice after treatment compared to control; of note, older control mice had significantly higher levels of IgE levels (728%) compared to young controls. Protein levels of VEGF and IL-6 in the ear tissue were significantly increased in young (1650% and 1500%, respectively) and old (362% and 125%, respectively) mice compared to control; levels were significantly higher levels in young treated mice compared to old treated mice. Luciferase signals were detected in the mesenteric lymph nodes, thymus and pancreas of treated mice. Older mice had significant higher levels of luciferase activity in the mesenteric lymph nodes and pancreas compared to young mice (control data not reported; there is a discrepancy between the figure legend and results text regarding whether the significance is from control or the young mice. Based on data presented this reviewer believes the significance is from comparison to the young group).

[14] 5160984: In a modified dermal LLNA study, male and female BALB/c mice (likely 8 animals/group, sex/group, number of males and females not specified) had 25ul of 25% phthalic anhydride (99.77% pure; in 4:1 acetone:olive oil [AOO]) or AOO alone applied to the dorsum of both ears on days 0, 1, and 2. On day 7, mice were sacrificed, and auricular lymph nodes were collected and weighed and made into single cell suspensions and counted. LN cells were then cultured to measure lymphocyte proliferation and cytokine production in vitro. Lymph nodes from 2 control animals were pooled due to the low number of cells obtained. Lymphocytes were incubated with 3H-thymidine for 24 hours, and proliferation was assessed using a liquid scintillation counter. For cytokine studies, lymphocytes were cultured with Con A (5 μg/ml) and 5 x10-5 M 2-mercaptoethanol for 24 hours, and IFN-γ and IL-4 concentrations were determined via ELISA.Significant increases in lymph node relative weight and lymphocyte cell number were seen compared to control (data were not shown). After culturing lymphocytes for 24 hours, a significant increase in lymphocyte proliferation was seen compared with the control (3H-thymidine incorporation). Significant increases in both IFN-γ and IL-4 were seen, compared with controls, in cultured lymphocytes. The induction of IL-4 was much more pronounced. The robust increase in IL-4 was similarly observed with the other known respiratory sensitizer, toluene-2,4-diisocyanate (TDI), which was also used in the study, whereas dinitrochlorobenzene (DNCB), a known contact sensitizer, showed limited IL-4 induction, but robust IFN-γ induction. The test substance was positive for sensitization in the modified dermal LLNA protocol tested. SI was not reported but could be estimated based on the figure presented.

Phthalic anhydride - Subchronic (>30-91 days)

Guideline and Animal Species, Strain, Sex	Exposure Route and Exposure Duration	Study-wide POD and Dose/ Concentration(s)	Summary	Major Limitations	Principal Target Organs/Systems and OQD*	Citation and HERO ID
Adherence to a test guideline or GLP were not specified. Monkey; Macaca fascicularis - [monkey]; Male	Intracutaneous injection 1 days/week 10 weeks Animals were also intracutaneously injected before and every 2 weeks during the study as part of the skin test; concentrations ranged from 10^-3 to 10^-7 mol/L phthalic anhydride and 10^-6 to 10^-10 mol/L phthalic anhydride-MSA	**POD: 0.0013 mg/kg bw (LOAEL, immuno) (0.000000047 mol)** 0, 0.000000047, 0.0000014mol/L	See footnotes for full summary [1]	Approximate doses in mg/kg bw were not provided. Only a range of starting bodyweights were provided, so an average bodyweight was used in the dose calculation. Starting age of the monkeys was not specified. No other endpoints were evaluated as part of this study. A LOAEL instead of a NOAEL was selected because effects were observed at the lower dose containing MSA, but not the higher dose without MSA. The text in Table II was not clearly legible, so a better copy of the paper on HERO should be obtained. The animals had been used for a previous study, however, the paper authors stated that that exposure was not likely to affect the PAD study based on control skin testing experiments.	Immune/Hematological: Medium	Biagini 1988 5180411
No guideline followed. Study done according to NCI protocols (predates NTP); Predates GLP Rat; Fischer 344 - [rat]; Both	Oral: Diet 7 weeks Administered ad libitum in the diet	**POD: 25000 ppm (NOAEL, dec. mean BW in males and females)** 0, 6200, 12500, 25000, 50000 ppm (in air, water, or food)	See footnotes for full summary [2]	Limited endpoints were evaluated and poor data reporting reduce the usefulness of this preliminary study.The study noted that animals were housed in the same room as other animals being treated with other chemicals, some of which are known to be volatile.	Nutritional/Metabolic: Medium	NCI 1979 63768

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Phthalic anhydride - Subchronic (>30-91 days)

Guideline and Animal Species, Strain, Sex	Exposure Route and Exposure Duration	Study-wide POD and Dose/ Concentration(s)	Summary	Major Limitations	Principal Target Organs/Systems and OQD*	Citation and HERO ID
No guideline followed. Study done according to NCI protocols (predates NTP); Predates GLP Mouse; B6C3F1 - [mouse]; Both	Oral: Diet 7 weeks Administered ad libitum in the diet	**POD: 50,000 ppm (NOAEL, no effects observed for any endpoint)** 0, 6200, 12500, 25000, 50000 ppm (in air, water, or food)	In a preliminary dose-range finding subchronic study, groups of B6C3F1 mice (5/sex) were administered phthalic anhydride in the diet at concentrations of 0, 6,200, 12,500, 25,000, and 50,000 ppm for 7 weeks. After treatment, animals were observed for 1 additional week prior to sacrifice. Limited endpoints evaluated included mortality and body weights measured twice weekly. Animals were necropsied following the observation period, and tissues (not specified) were examined for histopathologic findings. No mortalities were observed. Mean body weights of all treated animals (both sexes) remained within 10% of controls in all dose groups. No histopathological results were observed at 50,000 ppm; no results were reported for other dose groups.The doses of 0, 6,200, 12,500, 25,000, and 50,000 ppm were calculated to be equivalent to approximately 0, 934, 1875, 3750, and 7500 mg/kg-day using the following equation: ppm * food factor = mg/kg-bw/day, where the food factor is 0.15 for mouse. Study authors state that test substance loss from the diet was 2.59% (372 ppm) per day when stored at room temperature for two-weeks. Study authors further state that diets were prepared fresh every 1-1.5 weeks. Assuming fresh diet was prepared every 10 days, overall test substance loss was 25.9% over the 10 day period. Achieved doses in mg/kg-day accounting for 25.9% test substance loss were calculated to be: 0, 692, 1389, 2779, 5558 mg/kg-day. A NOAEL of 5558 mg/kg-day was identified (No LOAEL identified).	Limited endpoints were evaluated and poor data reporting reduce the usefulness of this preliminary study.The study noted that animals were housed in the same room as other animals being treated with other chemicals, some of which are known to be volatile.	Not applicable. No adverse effects observed at highst dose tested.: Medium	NCI 1979 63768

* Overall Quality Determination

[1] 5180411: Young adult male Macaca fascicularis monkeys received 0.2 mL subcutaneous inguinal injections of aluminum hydroxide plus the following solutions, weekly for 10 weeks: group 1, 200 ug phthalic anhydride-monkey serum albumin conjugate (PA-MSA) containing 4.7x10^-8 mol phthalic anhydride; group 2, 1.4x10^-6 mol phthalic anhydride; group 3, 200 ug MSA; and group 4, ethanol-saline solution. Phthalic anhydride was solubilized in ethanol-saline solution for these injections. Additionally, animals were intracutaneously injected on shaved areas of the chest and thorax with 100 uL of the following, before the study and every 2 weeks during the study, to evaluate skin reactions: 0.5% histamine (positive control); 10 mg/mL ethanol-saline, PBS, and MSA (negative controls); serial 10-fold dilutions of 10^-3 to 10^-7 mol/L phthalic anhydride; and serial 10-fold dilutions of 10^-6 to 10^-10 mol/L PA-MSA. Total serum IgE, specific IgE, and PA-MSA-specific IgE levels were measured at the baseline and every 2 weeks during the study. Skin reactions were examined 30 minutes following the intracutaneous injections and positive reactions were measured using a circular millimeter template (no other details provided). PA-MSA-specific IGE levels were significantly increased in group 1 (PA-MSA) after 4, 6, 8, and 10 weeks of injections. PA-MSA-specific IgE was also significantly increased in all groups when compared with their baseline values. No other significant changes in IgE levels were observed.Positive skin reactions were observed in group 1 (PA-MSA) following injections of PA-MSA at weeks 8 and 10. No other positive reactions were observed in other groups with phthalic anhydride alone or with PA-MSA. The LOAEL for this study is suggested as 4.7x10^-8 mol phthalic anhydride (calculated as equivalent to approximately 0.0013 mg/kg bw, based on starting bodyweights ranging from 4.5-6.0 kg (calculated avg. 5.25 kg) and a MW of 148.12 g/mol), based on increased PA-MSA-specific IgE levels. A histamine positive control was also tested for the skin reaction test. The most immunogenic test article was PAD reacted with MSA.

[2] 63768: In a preliminary subchronic study, groups of F344 rats (5/sex) were administered phthalic anhydride in the diet at concentrations of 0, 6,200, 12,500, 25,000, and 50,000 ppm for 7 weeks. After treatment, animals were observed for 1 additional week prior to sacrifice. Limited endpoints evaluated included mortality and body weights measured twice weekly. Animals were necropsied following the observation period, and tissues (not specified) were examined for histopathologic findings. No statistical analyses were described. No mortalities were observed. Mean body weights were decreased in both males (18% lower than controls) and females (20% lower than controls) at 50,000 ppm. 25,000 ppm was reported to be the lowest dose at which histopathologic findings were observed. Trace amounts of centrilobular cytoplasmic vacuolation were seen in the livers of 4/5 males at 25,000 ppm, but tissues were reported to be normal at 50,000 ppm (data not provided). The doses of 0, 6,200, 12,500, 25,000, and 50,000 ppm were calculated to be equivalent to approximately 0, 310, 625, 1250, and 2500 mg/kg-day using the following equation: ppm * food factor = mg/kg-bw/day, where the food factor is 0.05 for and old rat (note: age of rats was not specified in the study). Study authors state that test substance loss from the diet was 2.59% (372 ppm) per day when stored at room temperature for two-weeks. Study authors further state that diets were prepared fresh every 1-1.5 weeks. Assuming fresh diet was prepared every 10 days, overall test substance loss was 25.9% over the 10 day period. Achieved doses in mg/kg-day accounting for 25.9% test substance loss were calculated to be: 0, 230, 463, 926, 1853 mg/kg-day. A NOAEL of 926 mg/kg-day was identified based on reduced terminal body weight gain at the LOAEL of 1853 mg/kg-day.

Phthalic anhydride - Chronic (>91 days)

Guideline and Animal Species, Strain, Sex	Exposure Route and Exposure Duration	Study-wide POD and Dose/ Concentration(s)	Summary	Major Limitations	Principal Target Organs/Systems and OQD*	Citation and HERO ID
No guideline followed. Study done according to NCI protocols (pre-dates NTP); Pre-dates GLP Rat; Fischer 344 - [rat]; Both	Oral: Diet 105 weeks Animals were fed ad libitum. Food consumption measurements were not included in the study.	**POD: 7500 ppm (NOAEL, dec. BW in males); Phthalic anhydride was reported to be not carcinogenic** 0, 7500, 15000 ppm (in air, water, or food)	See footnotes for full summary [1]	Food consumption was not measured and no statements of palatability were provided. Since the only apparent treatment-related effect was a small decrease in body weight in high dose males throughout the study, it is unknown whether palatability could have been the cause. The study noted that animals were housed in the same room as other animals being treated with other chemicals, some of which are known to be volatile.	Nutritional/Metabolic: Medium	NCI 1979 63768
No guideline followed. Study done according to NCI protocols (pre-dates NTP); Pre-dates GLP Mouse; B6C3F1 - [mouse]; Both	Oral: Diet 105 weeks The reported TWA doses were 0, 16,346 and 32,692 ppm in males and 0, 12,019 and 24,038 ppm in females.Animals were fed ad libitum. Food consumption measurements were not included in the study.	**POD: 12019 ppm (LOAEL, dec. BW in males and females); Phthalic anhydride was reported to be not carcinogenic** 0, 12,019, 24,038 ppm (in air, water, or food)	See footnotes for full summary [2]	Food consumption was not measured and no statements of palatability were provided. Since the only apparent treatment-related effect was a small decrease in body weight in high dose males throughout the study, it is unknown whether palatability could have been the cause. The study noted that animals were housed in the same room as other animals being treated with other chemicals, some of which are known to be volatile.	Cancer/Carcinogenesis, Nutritional/Metabolic: Medium	NCI 1979 63768

* Overall Quality Determination

[1] 63768: In a cancer bioassay, groups of F344 rats (50/sex/test group, 20/sex for controls) were administered phthalic anhydride in the diet at reported nominal concentrations of 0, 7,500 and 15,000 ppm for 105 weeks. Endpoints evaluated included mortality, clinical signs (including palpitation for masses), and gross and microscopic examinations. Food and water intake were not recorded other endpoints (e.g., hematology, clinical chemistry, organ weights) were not included in the assay. No significant differences in survival were reported; however, survival of control males was lower (70%) than in the treatment groups (72% and 88% in low and high-dose males, respectively). Mean body weights of high-dose males were reported to be lower than controls. Data were presented as growth curves without measures of variance or indicators of statistical significance. Generally, mean body weights of high-dose males appeared to range approximately 7-10% less than controls throughout the study. Non-neoplastic lesions occurred with equal frequency and severity across groups and were generally expected for animals of this age and strain. No compound-related differences in the incidences of tumors in males were observed. In females, a statistically significant positive dose-related trend in incidences of alveolar/bronchiolar adenomas was observed but results of the Fisher exact tests for direct comparison were not significant. Doses of 0, 7,500 and 15,000 ppm were calculated by SRC to be equivalent to approximately 0, 375, and 750 mg/kg-day using the following equation: ppm * food factor = mg/kg-bw/day, where the food factor is 0.05 for an older rat. Study authors state that test substance loss from the diet was 2.59% (372 ppm) per day when stored at room temperature for two-weeks. Study authors further state that diets were prepared fresh every 1-1.5 weeks. Assuming fresh diet was prepared every 10 days, overall test substance loss was 25.9% over the 10 day period. Achieved doses in mg/kg-day accounting for 25.9% test substance loss were calculated to be: 278 and 556 mg/kg-day. A NOAEL of 278 mg/kg-day was identified based on reduced bodyweight at the LOAEL of 556 mg/kg-day. The test substance was considered to be negative for carcinogenicity under the conditions of this study.

[2] 63768: In a cancer bioassay, groups of B6C3F1 mice (50/sex/test group, 20/sex for controls) were administered phthalic anhydride in the diet at reported concentrations of 0, 25,000, and 50,000 ppm. Due to excessive weight loss, after 32 weeks, dietary concentrations were reduced to 0, 12,500 and 25,000 ppm in males and 0, 6,250 and 12,500 ppm in females. The reported TWA doses were 0, 16,346 and 32,692 ppm in males and 0, 12,019 and 24,038 ppm in females. Endpoints evaluated included monitoring for mortality, clinical signs (including palpitation for masses), and gross and microscopic examinations. Food and water intake were not recorded which significantly impacts the ability to accurately determine dosing. Other endpoints (e.g., hematology, clinical chemistry, organ weights) were not included in the assay. No significant effect on mortality or clinical signs were observed. Mean body weights were reported to be decreased in all treatment groups from both sexes, compared with controls and depressions in body weight gain were dose-related, occurring throughout the study period. Growth curves were provided without measures of variance or indicators of statistical significance. Based on the graph displayed, body weights were decreased by up to approximately 11% in mid-dose animals and up to approximately 28% in high dose animals, compared with controls. Both non-neoplastic lesions and incidences of tumors occurred with equal frequency and severity across groups and were generally expected for animals of this age and strain. TWA doses of 0, 16,346 and 32,692 ppm in males and 0, 12,019 and 24,038 ppm in females were calculated to be equivalent to 0, 2452, and 4904 mg/kg/day in males and 0, 1803, and 3606 mg/kg-day in females using the following equation: ppm * food factor = mg/kg-bw/day, where the food factor is 0.15 for mouse. Study authors state that test substance loss from the diet was 2.59% (372 ppm) per day when stored at room temperature for two-weeks. Study authors further state that diets were prepared fresh every 1-1.5 weeks. Assuming fresh diet was prepared every 10 days, overall test substance loss was 25.9% over the 10 day period. Achieved doses in mg/kg-day accounting for 25.9% test substance loss were calculated to be: 1,817 and 3,634 mg/kg-day for males and 1,336 and 2,672 mg/kg-day for females. A LOAEL of 1336 mg/kg-day was identified (no NOAEL identified).The study author reported phthalic anhydride to be not carcinogenic.

Phthalic anhydride - Reproductive/Developmental

Guideline and Animal Species, Strain, Sex	Exposure Route and Exposure Duration	Study-wide POD and Dose/ Concentration(s)	Summary	Major Limitations	Principal Target Organs/Systems and OQD*	Citation and HERO ID
"This research was conducted in accordance with the Principles of Laboratory Animal Care (NIH publication, revised in 1985). All the study experiments were approved by the Animal Research Ethics Board and approved prospectively by the Ethics Committee ofIlam University of Medical Sciences, Iran." Rat; Wistar - [rat]; Female	Oral: Diet 10 days Gestation day 7-16	**POD: 1763 mg/kg/day (LOAEL, developmental)** 0, 1763, 2981 mg/kg-bw/day F0 - gestation, day 7-day 16	See footnotes for full summary [1]	Maternal effects (body weight gain, food consumption, survival) not reported; Developmental and reproductive outcomes beyond pup body weight not reported; For most outcomes, authors did not report if measured in male, female, or combined F1 offspring; Fewer dams per dose group than recommended by OECD TG No. 414 (n=8 vs. n=20 in OECD TG 414); Exposure duration did not include late gestation, as recommended by current OECD TG No. 414	Reproductive/Developmental: High	Rahmani et al. 2015 3071054

* Overall Quality Determination

[1] 3071054: Apical and mechanistic POD: 1763 mg/kg/day (LOAEL for developmental and enzymatic activity)Pregnant Wistar rats (8/group) were provided a diet containing 0, 2.5% or 5.0% phthalic acid (0, 1763 or 2981 mg/kg/day, respectively) from gestational day 7-16. At 3 months of age, body weight, blood pressure and heart rate were recorded in the offspring. Offspring were sacrificed at 3 months of age and the heart was removed and weighed. The proximal part of the septal branch of the left descending coronary artery and thoracic aorta were collected for morphology and geometry measurements (inner diameter, arterial wall thickness, volume densities of endothelial cells, subendothelial matrix, smooth muscle cells and extracellular matrix). Other endpoints evaluated included serum levels of malondialdehyde (MDA) levels and activities of glutathione peroxidase (GPx), superoxide dismutase (SOD) and nitric oxide synthesis (NOS) in the heart. Body weight of offspring were significantly decreased in the low (-14%) and high (-25%) dose groups compared to control. Significant increases in blood pressure were seen in the low (+5%) and high (+12%) dose group and heart rate (+9%) in the high dose group compared control. Absolute heart weights were significantly decreased in low (-12%) and high (-19%) dose groups and relative heart weight increased in high dose group (+8%) compared to control. A significant increases in wall thickness and cross-sectional area were seen in the thoracic aorta and coronary artery in the low and high dose groups. The inner diameter of the coronary artery, but not the thoracic aorta, was significantly decreased in both dose groups compared to control. The ratio of wall thickness to inner diameter was significantly increased in the thoracic aorta and coronary artery in both dose groups compared to control. Volume densities were not reported. Increased oxidative stress was seen in heart of prenatally treated offspring, as determined by a significant dose-related increase in MDA levels and decreased in SOD levels in both dose groups compared to control. GPx levels were decreased in both dose groups, but only reached significance in the high dose group. NOS activity in the heart was significantly decreased in a dose related manner in both dose groups compared to control.

Epidemiology Extraction Table: Cancer/Carcinogenesis

Measured Effect/ Endpoints	Study Population	Exposure	Results	Overall Quality Determination	Citation and HERO ID
Lung cancer mortality Study Design: Case-Control Health Effect: Lung/Respiratory	occupational male Milano Province, Italy; 43 cases of dying by lung cancer, 99 referents, 1/1/1976-12/31/1979	Occupational exposure (phthalic anhydride, acetylene, and their derivatives, soot, phthalates and other suspected carcinogens); employed at the SISAS plant for 2-20 years (S+), employed at a job likely to have exposure to lung carcinogens (E+), or no occupational exposure (E-)	Standardized OR (dying due to lung cancer, employed at SISAS: 5.6 (95% CI 1.9-16.2) compared to referents Comments: Risk ratios were not calculated for exposure specifically to phthalic anhydride.	Medium	Riboli et al. 1983 63774
Malignant skin tumors Study Design: Cross-Sectional Health Effect: Cancer/Carcinogenesis	occupational male & female 174 employees of a phthalic anhydride plant, 1978	Phthalic anhydride (quantitative information not reported)	Prevalence of skin condition per 100 persons in study population vs. USA general population:Malignant skin tumors: 0.0 vs. 0.6 Comments: Outcome data comes from HEROID 68305.USA general population prevalence originated from 1/26/1977 National Center for Health Statistics data	Low	TOMA 1978 1480908
Sputum cytology, urine cytology Study Design: Cross-Sectional Health Effect: Cancer/Carcinogenesis	occupational male & female 453 Koppers Coal Tar plants employees (105 from an exposed plant, 14 workers exposed directly to phthalic anhydride), 1979	Occupational exposure to phthalic anhydride (exposure levels not reported)	Incidence of abnormal findings among workers from the plant exposed to phthalic anhydride:Sputum cytology: 0/105Urine cytology: 0/105No formal statistical analyses were performed.	Low	TOMA 1981 5299399
Malignant skin tumors Study Design: Cross-Sectional Health Effect: Cancer/Carcinogenesis	occupational male & female 139 employees (129 males, 10 females) of a phthalic anhydride plant, 1981	Phthalic anhydride, level not reported	Prevalence of skin condition per 100 persons in study population vs. USA general population:Malignant skin tumors: 0.0 vs. 0.6 Comments: USA general population prevalence originated from 1/26/1977 National Center for Health Statistics data	Low	TOMA 1982 63805

Epidemiology Extraction Table: Hepatic/Liver

Measured Effect/ Endpoints	Study Population	Exposure	Results	Overall Quality Determination	Citation and HERO ID
Total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides Study Design: Cohort (Prospective) Health Effect: Nutrition & Metabolic	children (2-18y) male & female 757 mother/child pairs from a subgroup of the Generation R Study in Rotterdam, the Netherlands (2004-2005); children 10 years of age	Phthalic acid, median (1st, 2nd, and 3rd trimester): 345.9, 865.5, and 391.3 nmol/L, respectively urine	Regression coefficient (95% CI) for difference in triglycerides per 1-IQR increase in third trimester phthalic acid in boys:0.20 (0.07, 0.34), p-value for sex interaction = 0.06Regression coefficient (95% CI) for difference in triglycerides per 1-IQR increase in second trimester phthalic acid in girls:-0.14 (-0.27, -0.00), p-value for sex interaction = 0.12No other statistically significant results.	High	Sol et al. 2020 6957607
Lactate dehydrogenase (LDH), indirect bilirubin, albumin, gamma-glutamyl transferase (GGT), alkaline phosphatase, direct bilirubin Study Design: Cross-Sectional Health Effect: Hepatic/Liver	occupational male & female 453 Koppers Coal Tar plants employees (105 from an exposed plant, 14 workers exposed directly to phthalic anhydride), 1979	Occupational exposure to phthalic anhydride (exposure levels not reported)	Incidence of abnormal findings among workers from the plant exposed to phthalic anhydride:LDH: 5/104Indirect bilirubin: 5/104Albumin: 0/104GGT: 10/104Alkaline phosphatase: 2/104Direct bilirubin: 0/104No formal statistical analyses were performed.	Low	TOMA 1981 5299399

Epidemiology Extraction Table: Immune/Hematological

Measured Effect/ Endpoints	Study Population	Exposure	Results	Overall Quality Determination	Citation and HERO ID
Self-reported ocular and respiratory symptoms, skin prick test, serum antibodies against phthalic acid-human serum albumin hapten conjugate Study Design: Cohort Health Effect: Immune/Hematological	occupational male & female 60 workers (58 men, 2 women) exposed to phthalic anhydride in 2 plants producing alkyl and/or unsaturated polyester resins compared with 22 male workers employed at a food-processing plant and 30 postal clerks (for specific IgM analysis only).	Exposure assessed as employment with exposure to phthalic anhydride. TWA (mg/m3), 6.6 during PA loading (6.1 - 6.8); <0.1 during other tasks.	No significant difference between exposed and controls in prevalence of chronic bronchitis, skin prick test result, serum total and specific serum levels of IgE and IgM, or total serum IgG. Significant increase in specific IgG between heavy- and low-exposure groups (p=0.01). Five (14%) heavily exposed workers self-reported asthma; no low-exposed workers reported having asthma. In subjects with symptoms of rhinoconjunctivitis, there was a significantly decreased total IgG (medians: 7.7 mg/L vs. 9.8 mg/L in controls; p = 0.01). Those with symptoms of asthma, had significantly increased specific IgG levels (medians: 4.6 mg/L vs. 1.8 mg/L in controls; p=0.005). Comments: Rhinitis was reported in 14 (40%) and 5 (20%) in heavy-exposed subjects and low-exposed subjects, respectively; rhinoconjunctivitis was reported in 16 (46%) and 3 (12%) in heavy- and low-exposed subjects, respectively; conjunctivitis was reported in 6 (17%) and 5 (20%) in heavy- and low-exposed subjects, respectively.	Low	Nielsen et al. 1988 5176341
Red blood cells, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, reticulocyte count, white blood cells, polymorphonuclear leukocytes, lymphocytes, monocytes, basophils, eosinophils, IgE, IgM, IgA, IgG Study Design: Cross-Sectional Health Effect: Immune/Hematological	occupational male & female 453 Koppers Coal Tar plants employees (105 from an exposed plant, 14 workers exposed directly to phthalic anhydride), 1979	Occupational exposure to phthalic anhydride (exposure levels not reported)	Incidence of abnormal findings among workers from the plant exposed to phthalic anhydride:RBC: 1/104HGB: 2/104HCF: 1/104MCV: 2/104MCH: 0/104MCHC: 0/104WBC: 2/104Polymorphonuclear leukocytes: 5/104Lymphocytes: 9/104Monocytes: 0/104Basophils: 0/104Eosinophils: 11/104Incidence of abnormal findings in workers specifically exposed to phthalic anhydride vs. workers exposed to only coal tarIgE: 1/14 vs. 5/81IgM: 0/14 vs. 2/81IgA: 0/14 vs. 2/81IgG: 0/14 vs. 0/81No formal statistical analyses were performed.	Low	TOMA 1981 5299399

Epidemiology Extraction Table: Irritation

Measured Effect/ Endpoints	Study Population	Exposure	Results	Overall Quality Determination	Citation and HERO ID
Self-reported ocular and respiratory symptoms Study Design: Cohort Health Effect: Irritation	occupational male & female 60 workers (58 men, 2 women) exposed to phthalic anhydride in 2 plants producing alkyl and/or unsaturated polyester resins compared with 22 male workers employed at a food-processing plant.	Exposure assessed as employment with exposure to phthalic anhydride. TWA (mg/m3), 6.6 during PA loading (6.1 - 6.8); <0.1 during other tasks.	Rhinitis was reported in 14 (40%) of heavy-exposed subjects and 5 (20%) of low-exposed subjects; rhinoconjunctivitis was seen in 16 (46%) and 3 (12%) in heavy- and low-exposed subjects, respectively; conjunctivitis was seen in 6 (17%) and 5 (20%) in heavy- and low-exposed subjects, respectively; significance of the differences between exposure groups were not reported. No results were reported for the control group. 6 (17%) of heavily exposed subjects had chronic bronchitis and one (4%) of low exposed workers had chronic bronchitis; the difference was not statistically significant. Comments: Symptoms of chronic bronchitis are also considered under lung/respiratory outcomes	Low	Nielsen et al. 1988 5176341

Epidemiology Extraction Table: Lung/Respiratory

Measured Effect/ Endpoints	Study Population	Exposure	Results	Overall Quality Determination	Citation and HERO ID
Respiratory outcomes; chronic bronchitis, asthma Study Design: Cohort Health Effect: Lung/Respiratory	occupational male & female 60 workers (58 men, 2 women) exposed to phthalic anhydride in 2 plants producing alkyl and/or unsaturated polyester resins compared with 22 male workers employed at a food-processing plant.	Exposure assessed as employment with exposure to phthalic anhydride. TWA (mg/m3), 6.6 during PA loading (6.1 - 6.8); <0.1 during other tasks.	No significant difference between exposed and controls in self-reported prevalence of chronic bronchitis; 5 (14%) of workers heavily exposed (loaders) self-reported asthma at some point during occupational exposure; no low-exposed workers reported having asthma. Comments: Symptoms of chronic bronchitis and asthma are also considered under irritation and immunological	Medium	Nielsen et al. 1988 5176341
Lung cancer mortality Study Design: Case-Control Health Effect: Lung/Respiratory	occupational male Milano Province, Italy; 43 cases of dying by lung cancer, 99 referents, 1/1/1976-12/31/1979	Occupational exposure (phthalic anhydride, acetylene, and their derivatives, soot, phthalates and other suspected carcinogens); employed at the SISAS plant for 2-20 years (S+), employed at a job likely to have exposure to lung carcinogens (E+), or no occupational exposure (E-)	Standardized OR (dying due to lung cancer, employed at SISAS: 5.6 (95% CI 1.9-16.2) compared to referents Comments: Risk ratios were not calculated for exposure specifically to phthalic anhydride.	Medium	Riboli et al. 1983 63774
Forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1), abnormal chest x-ray findings Study Design: Cross-Sectional Health Effect: Lung/Respiratory	occupational male & female 453 Koppers Coal Tar plants employees (105 from an exposed plant, 14 workers exposed directly to phthalic anhydride), 1979	Occupational exposure to phthalic anhydride (exposure levels not reported)	Incidence of abnormal findings among workers from the plant exposed to phthalic anhydride:FVC: 8/105FEV1: 5/105Chest X-Ray: 1/105No formal statistical analyses were performed.	Low	TOMA 1981 5299399
Asthma, spirometry, chronic productive bronchitis, respiratory symptoms Study Design: Cross-Sectional Health Effect: Lung/Respiratory	occupational male & female 48 (46 male, 2 female) current and 70 (sex not reported) former resin plant employees	TWA ranging 3 to 13 mg/m3	Asthma was observed in 15 former employees and 6 current employees, primarily (71%) of late type; Work-related rhinitis reported among current and former employees (24%); chronic productive bronchitis reported among current (4%) and former (11%) employees; abnormal spirometry values for one current asthmatic employee	Low	Wernfors et al. 1986 5176303
Asthma, eosinophils, serum immunoglobulins Study Design: Cross-Sectional Health Effect: Lung/Respiratory	occupational male & female 48 (46 male, 2 female) current and 70 (sex not reported) former resin plant employees	TWA ranging 3 to 13 mg/m3	Asthma was observed in 15 former employees and 6 current employees, primarily (71%) of late type; elevated serum IgE in two asthmatic and two non-asthmatic employees; elevated eosinophils in two asthmatic employees	Low	Wernfors et al. 1986 5176303

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Epidemiology Extraction Table: Lung/Respiratory

Measured Effect/ Endpoints	Study Population	Exposure	Results	Overall Quality Determination	Citation and HERO ID
Skin prick test, P-K test Study Design: Cross-Sectional Health Effect: Lung/Respiratory	occupational male & female 48 (46 male, 2 female) current and 70 (sex not reported) former resin plant employees	TWA ranging 3 to 13 mg/m3	Positive skin-prick test for 2/3 currently employed asthmatics and 1/6 former asthmatic employees; positive P-K tests for two current asthmatic employees	Low	Wernfors et al. 1986 5176303

Epidemiology Extraction Table: Mortality

Measured Effect/ Endpoints	Study Population	Exposure	Results	Overall Quality Determination	Citation and HERO ID
Lung cancer mortality Study Design: Case-Control Health Effect: Lung/Respiratory	occupational male Milano Province, Italy; 43 cases of dying by lung cancer, 99 referents, 1/1/1976-12/31/1979	Occupational exposure (phthalic anhydride, acetylene, and their derivatives, soot, phthalates and other suspected carcinogens); employed at the SISAS plant for 2-20 years (S+), employed at a job likely to have exposure to lung carcinogens (E+), or no occupational exposure (E-)	Standardized OR (dying due to lung cancer, employed at SISAS: 5.6 (95% CI 1.9-16.2) compared to referents Comments: Risk ratios were not calculated for exposure specifically to phthalic anhydride.	Medium	Riboli et al. 1983 63774

Epidemiology Extraction Table: Nutrition & Metabolic

Measured Effect/ Endpoints	Study Population	Exposure	Results	Overall Quality Determination	Citation and HERO ID
obesity (BMI >= 85th percentile) Study Design: Cross-Sectional Health Effect: Nutrition & Metabolic	children (2-18y) female 127 Korean girls, April-September 2011, ages 6-14 years	Phthalic acid (PA) in urine:Controls: mean (ng/mL) 90.76Cases: mean (ng/mL) 213.37Phthalic acid (PA) in serum:Controls: mean (ng/mL) 93.48Cases: mean (ng/mL) 129.72 other Biomonitoring matrix: Serum and urine	Significantly higher urinary PA levels in obese patients (213.37 ng/mL) compared to controls (90.76 ng/mL), p-value=0.008Significantly higher serum PA levels in obese patients (129.72 ng/mL) compared to controls (93.48 ng/mL), p-value=0.024	Medium	Choi et al. 2014 2510764
Glucose and Insulin concentrations Study Design: Cohort (Prospective) Health Effect: Nutrition & Metabolic	children (2-18y) male & female 757 mother/child pairs from a subgroup of the Generation R Study in Rotterdam, the Netherlands (2004-2005); children 10 years of age	Phthalic acid, median (1st, 2nd, and 3rd trimester): 345.9, 865.5, and 391.3 nmol/L, respectively urine	Regression coefficient (95% CI) for difference in glucose per 1-IQR increase in second trimester phthalic acid in boys:-0.15 (-0.30, -0.01), p-value for sex interaction = 0.15	High	Sol et al. 2020 6957607
BMI, weight change rate Study Design: Cohort (Prospective) Health Effect: Nutrition & Metabolic	adults female 977 female nurses were included in this study, but phthalic acid concentrations were not available for 144 of the participants, Nurses' Health Study (NHS) and NHSII cohorts, United States, 1976 and 1989, respectively, age 53-79 years and 32-52 years, respectively, at the time of urine collection	Urinary phthalic acid, median concentration (nmol/L): Q1 = 212 Q2 = 369Q3 = 641Q4 = 1,326 urine	Phthalic acid concentrations were significantly, positively associated with baseline BMI (p-trend=0.02) and faster bodyweight gain during the follow-up (p-trend=0.001). Least square means (95% CI) of baseline BMI within each quartile of phthalic acid:Q1 = 25.5 (24.6 -26.3)Q2 = 26.1 (25.3-26.9)Q3 = 25.6 (24.8 - 26.4)Q4 = 27.0 (26.1-27.8)p-trend = 0.02Annual weight change (95% CI) rate per quartile of phthalic acidQ2 vs. Q1 = 0.19 (0.02 - 0.36)Q3 vs. Q1 = 0.21 (0.04 - 0.38)Q4 vs. Q1 = 0.33 (0.15 - 0.50)p-trend = 0.001	Medium	Song et al. 2014 2345937
Type 2 Diabetes (physician-diagnosis, confirmed by meeting American Diabetes Association criteria) Study Design: Case-Control (Nested) Health Effect: Nutrition & Metabolic	adults female Nurses' Health Study ()1976-2008), United States, 971 case-control pairs (all women)	NHS quartiles of phthalic acid exposure median (range) (ug/L)Q1 = 31.9 (0.9, 41.0)Q2 = 55.5 (41.3, 69.7)Q3 = 86.7 (70.1, 112.9)Q4 = 197.8 (114.9, 1846.7)NHS II quartiles of phthalic acid exposure median (range) (ug/L)Q1 = 35.9 (0.9, 51.8)Q2 = 64.5 (51.9, 8.3)Q3 = 113.6 (85.4, 156.8)Q4 = 225.5 (158.6, 2295.3) urine	OR (95% CI) for T2D comparing different quartiles of phthalic acid among NHS participants:Q2 vs. Q1 = 1.37 (0.71, 2.64)Q3 vs. Q1 = 1.23 (0.63, 2.42)Q4 vs. Q1 = 1.61 (0.79, 3.29)p-trend = 0.26OR (95% CI) for T2D comparing different quartiles of phthalic acid among NHS II participants:Q2 vs. Q1 = 1.56 (0.90, 2.71)Q3 vs. Q1 = 2.13 (1.19, 3.79)Q4 vs. Q1 = 1.77 (0.97, 3.23)p-trend = 0.19OR (95% CI) for T2D comparing the highest and lowest quartiles of phthalic acid, pooling both cohorts together:1.70 (1.08, 2.70)I^2 = 0.0%, p = 0.84	High	Sun et al. 2014 2345994

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Epidemiology Extraction Table: Nutrition & Metabolic

Measured Effect/ Endpoints	Study Population	Exposure	Results	Overall Quality Determination	Citation and HERO ID
Serum CO2, serum triglycerides, serum methemoglobulin, serum cholesterol, serum glucose, urine phenols Study Design: Cross-Sectional Health Effect: Nutrition & Metabolic	occupational male & female 453 Koppers Coal Tar plants employees (105 from an exposed plant, 14 workers exposed directly to phthalic anhydride), 1979	Occupational exposure to phthalic anhydride (exposure levels not reported)	Incidence of abnormal findings among workers from the plant exposed to phthalic anhydride:CO2: 0/104Triglycerides: 15/104Methemoglobulin: 0/104Glucose: 1/104Cholesterol: 1/104Urine phenols: 6/104No formal statistical analyses were performed.	Low	TOMA 1981 5299399

Epidemiology Extraction Table: Ocular & Sensory

Measured Effect/ Endpoints	Study Population	Exposure	Results	Overall Quality Determination	Citation and HERO ID
conjunctivitis Study Design: Cohort Health Effect: Ocular & Sensory	occupational male & female 60 workers (58 men, 2 women) exposed to phthalic anhydride in 2 plants producing alkyl and/or unsaturated polyester resins compared with 22 male workers employed at a food-processing plant.	Exposure assessed as employment with exposure to phthalic anhydride. TWA (mg/m3), 6.6 during PA loading (6.1 - 6.8); <0.1 during other tasks.	Conjunctivitis reported among 46% of heavily exposed workers and 20% of low exposed workers, no conjunctivitis symptoms reported among unexposed workers Comments: Symptoms of chronic bronchitis and asthma are also considered under irritation and immunological	Low	Nielsen et al. 1988 5176341

Epidemiology Extraction Table: Renal/Kidney

Measured Effect/ Endpoints	Study Population	Exposure	Results	Overall Quality Determination	Citation and HERO ID
ureamic pruritus score Study Design: Case-Control Health Effect: Renal/Kidney	adults nan 21 adult hemodialysis patients	Phthalic acid, Mean (ug/ml) Pre-Hemodialysis: 0.194, Post-Hemodialysis: 0.122 blood, serum, or plasma	No correlation found between phthalic acid and ureamic pruritus score; no significant difference between phthalic acid concentrations between cases and controls; phthalic acid concentrations significantly decreased post hemodialysis (from 0.194 +/- 0.101 to 0.122 +/- 0.078 ug/ml, P=0.00068).	Low	Mettang et al. 1996 673485
Blood urea nitrogen, cellular casts in urine, red blood cells in urine, white blood cells in urine, serum total protein, urine albumin, hyaline casts in urine Study Design: Cross-Sectional Health Effect: Renal/Kidney	occupational male & female 453 Koppers Coal Tar plants employees (105 from an exposed plant, 14 workers exposed directly to phthalic anhydride), 1979	Occupational exposure to phthalic anhydride (exposure levels not reported)	Incidence of abnormal findings among workers from the plant exposed to phthalic anhydride:BUN: 2/104Cellular casts in urine: 0/104RBC in urine: 8/104WBC in urine: 12/104Albumin PH: 1/104No formal statistical analyses were performed.	Low	TOMA 1981 5299399

Epidemiology Extraction Table: Reproductive/Developmental

Measured Effect/ Endpoints	Study Population	Exposure	Results	Overall Quality Determination	Citation and HERO ID
Hypospadias Study Design: Case-Control Health Effect: Reproductive/Developmental	infants (birth to 2y) male 80 controls, 80 hypospadias patients (and 40 mothers of patients) in Korea	Mean PA in plasma (ng/mL): Controls = 20.23Cases = 38.82Mothers of cases = 124.24Mean PA in urine (ng/mL):Controls = 326.78Cases =244.51Mothers of cases = 231.15 blood, serum, or plasma	PA in plasma was significantly associated with hypospadias (p=0.006), direction of effect not reported. PA was reported to be 1.92 times higher in the patient group compared to the control group in the text, although this is contradicted in the table.	Uninformative	Choi et al. 2012 1332536
time to pregnancy Study Design: nan Health Effect: Reproductive/Developmental	nan Generation R Study (2004-2010), Netherlands, 877 pregnant women	Phthalic acid, Median (ng/mL) 55.59	fecundability ratio for phthaltic acid; FR=0.96 (CI: 0.90-1.02). fecundability ratio among those with inadequate folic acid supplement use; FR=0.88 (CI: 0.79-0.99, p<0.05). fecundability ratio among those with folic acid supplement use; FR=0.99 (CI:0.91-1.08)	High	Philips et al. 2018 4728822
pre-eclampsia Study Design: Cohort (Prospective) Health Effect: Reproductive/Developmental	pregnant women female Generation R Study Cohort (2004-2010), Netherlands, 1233 pregnant women	Phthalic Acid, median (ng/ml) 56.99 urine	No significant effects	High	Philips et al. 2018 5043413
soluble fms-like tyrosine kinase-1 : placental growth factor ratio Study Design: Cohort (Prospective) Health Effect: Reproductive/Developmental	pregnant women female Generation R Study Cohort (2004-2010), Netherlands, 1233 pregnant women	Phthalic Acid, median (ng/ml) 56.99 urine	No significant effects	High	Philips et al. 2018 5043413
umbilical artery pulsatility index Study Design: Cohort (Prospective) Health Effect: Reproductive/Developmental	pregnant women female Generation R Study Cohort (2004-2010), Netherlands, 1233 pregnant women	Phthalic Acid, median (ng/ml) 56.99 urine	No significant effects	High	Philips et al. 2018 5043413
uterine artery resistance index Study Design: Cohort (Prospective) Health Effect: Reproductive/Developmental	pregnant women female Generation R Study Cohort (2004-2010), Netherlands, 1233 pregnant women	Phthalic Acid, median (ng/ml) 56.99 urine	No significant effects	High	Philips et al. 2018 5043413
notching Study Design: Cohort (Prospective) Health Effect: Reproductive/Developmental	pregnant women female Generation R Study Cohort (2004-2010), Netherlands, 1233 pregnant women	Phthalic Acid, median (ng/ml) 56.99 urine	No significant effects	High	Philips et al. 2018 5043413

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Epidemiology Extraction Table: Reproductive/Developmental

Measured Effect/ Endpoints	Study Population	Exposure	Results	Overall Quality Determination	Citation and HERO ID
placental weight Study Design: Cohort (Prospective) Health Effect: Reproductive/Developmental	pregnant women female Generation R Study Cohort (2004-2010), Netherlands, 1233 pregnant women	Phthalic Acid, median (ng/ml) 56.99 urine	No significant effects	High	Philips et al. 2018 5043413
gestational hypertension Study Design: Cohort (Prospective) Health Effect: Reproductive/Developmental	pregnant women female Generation R Study Cohort (2004-2010), Netherlands, 1233 pregnant women	Phthalic Acid, median (ng/ml) 56.99 urine	No significant effects	High	Philips et al. 2018 5043413

Epidemiology Extraction Table: Sensitization

Measured Effect/ Endpoints	Study Population	Exposure	Results	Overall Quality Determination	Citation and HERO ID
skin prick test and PA-HSA-specific immunoglobulins Study Design: Cohort Health Effect: Sensitization	occupational male & female 60 workers (58 men, 2 women) exposed to phthalic anhydride in 2 plants producing alkyl and/or unsaturated polyester resins compared with 22 male workers employed at a food-processing plant.	Exposure assessed as employment with exposure to phthalic anhydride. TWA (mg/m3), 6.6 during PA loading (6.1 - 6.8); <0.1 during other tasks.	No significant association between PA-HSA specific IgE and PA exposure, four workers with specific IgE above the highest referent (RAST ratio 2.2) with one exhibiting rhinitis and another with a history of work-related asthma attacks Comments: Symptoms of chronic bronchitis and asthma are also considered under irritation and immunological	Medium	Nielsen et al. 1988 5176341

Epidemiology Extraction Table: Skin and Connective Tissue

Measured Effect/ Endpoints	Study Population	Exposure	Results	Overall Quality Determination	Citation and HERO ID
Fungal skin infection, acne, benign growths, malignant skin tumors, keratosis, eczema, folliculitis Study Design: Cross-Sectional Health Effect: Skin and Connective Tissue	occupational male & female 174 employees of a phthalic anhydride plant, 1978	Phthalic anhydride (quantitative information not reported)	Prevalence of skin condition per 100 persons in study population vs. USA general population:Fungal skin infections: 0.0 vs. 8.1Acne: 0.0 vs. 8.5Benign growths: 2.7 vs. 3.8Malignant skin tumors: 0.0 vs. 0.6Keratosis: 0.7 vs. 1.0Eczema: 2.0 vs. 1.8Folliculitis: 0.0 vs. 0.8Other skin conditions: 2.7 vs. 19.4Total skin conditions: 8.1 vs. 44.0 Comments: Outcome data comes from HEROID 68305.USA general population prevalence originated from 1/26/1977 National Center for Health Statistics data	Low	TOMA 1978 1480908
Benign skin growths, other skin conditions (keratosis, eczema, folliculitis) Study Design: Cross-Sectional Health Effect: Immune/Hematological	occupational male & female 453 Koppers Coal Tar plants employees (105 from an exposed plant, 14 workers exposed directly to phthalic anhydride), 1979	Occupational exposure to phthalic anhydride (exposure levels not reported)	Incidence of abnormal findings among workers from the plant exposed to phthalic anhydride:Benign skin growths: 1/92Other skin findings: 20/92No formal statistical analyses were performed.	Low	TOMA 1981 5299399
Fungal skin infection, acne, benign growths, malignant skin tumors, keratosis, eczema, folliculitis Study Design: Cross-Sectional Health Effect: Skin and Connective Tissue	occupational male & female 139 employees (129 males, 10 females) of a phthalic anhydride plant, 1981	Phthalic anhydride, level not reported	Prevalence of skin condition per 100 persons in study population vs. USA general population:Fungal skin infections: 0.0 vs. 8.1Acne: 0.7 vs. 8.5Benign growths: 0.0 vs. 3.8Malignant skin tumors: 0.0 vs. 0.6Keratosis: 0.0 vs. 1.0Eczema: 0.7 vs. 1.8Folliculitis: 1.5 vs. 0.8Other skin conditions: 4.4 vs. 19.4Total skin conditions: 7.3 vs. 44.0 Comments: USA general population prevalence originated from 1/26/1977 National Center for Health Statistics data	Low	TOMA 1982 63805