Reconsideration of Three Chemicals Listed under Proposition 65 as Known to Cause Reproductive Toxicity

Chemicals Listed via the Labor Code Mechanism:

Hexafluoroacetone
Phenylphosphine

Chemical Listed via the Authoritative Bodies Mechanism:

Chlorsulfuron

Office of Environmental Health Hazard Assessment
California Environmental Protection Agency

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Contents

Background

Proposition 65[1] requires the State to publish a list of chemicals known to cause cancer or reproductive toxicity. This list must be updated at least once a year. Reproductive toxicity includes developmental toxicity, and female and male reproductive toxicity. Chemicals added to the list as known to cause reproductive toxicity affect one or more of these endpoints.

Two of the chemicals covered in this document, hexafluoroacetone and phenylphosphine, were added to the list as known to cause reproductive toxicity because they were identified by reference as such in the California Labor Code (see Table 1 below). The third chemical covered in the document, chlorsulfuron, was added to the list as known to cause reproductive toxicity based on formal identification by the U.S. Environmental Protection Agency (U.S.EPA), an authoritative body[2], that the chemical causes reproductive toxicity (see Table 2 below). Proposition 65 thus required their inclusion on the list, as discussed in greater detail below. There are two additional ways for a chemical to be added to the Proposition 65 list: 1) The Developmental and Reproductive Toxicant Identification Committee (DARTIC) finds that the chemical has been clearly shown to cause reproductive toxicity. 2) An agency of the state or federal government requires that it be labeled or identified as causing reproductive toxicity.

Reason for Reconsideration of Listing: Labor Code Chemicals

Because of recent changes in federal regulations, hexafluoroacetone and phenylphosphine no longer meet the criteria for inclusion on the list on the basis of the Labor Code mechanism. Each of these chemicals is being presented to the DARTIC for a decision as to whether it has been clearly shown through scientifically valid testing according to generally accepted principles to cause reproductive toxicity. If the Committee makes that determination, the chemical will remain on the list. Conversely, if

[1] The Safe Drinking Water and Toxic Enforcement Act of 1986: Health and Safety Code section 25249.5 *et seq.,* passed by voter initiative.

[2] Title 27, California Code of Regulations, section 25306(l). The authoritative bodies are: U.S. Environmental Protection Agency, U.S. Food and Drug Administration, National Institute for Occupational Safety and Health, National Toxicology Program solely as to final reports of the National Toxicology Program's Center for Evaluation of Risks to Human Reproduction, and International Agency for Research on Cancer solely as to transplacental carcinogenicity.

the Committee determines the chemical has not been clearly shown to cause reproductive toxicity, the chemical will be delisted.

Hexafluoroacetone and phenylphosphine were added to the list in 2008 and 2009, respectively, on the basis of Threshold Limit Values (TLV) developed by the American Conference of Governmental Industrial Hygienists (ACGIH) that were based on reproductive or developmental toxicity. They were listed as known to cause reproductive toxicity based on their ACGIH TLV. The TLV provided a basis for listing via the Labor Code because:

- Proposition 65 provides that the list of chemicals known to the state to cause reproductive toxicity "shall include at a minimum those substances identified by reference in Labor Code Section 6382(b)(1) and those substances identified additionally by reference in Labor Code Section 6382(d)[3]".

- California Labor Code Section 6382(d) further provides that "…any substance within the scope of the federal Hazard Communication Standard (29 C.F.R. Section 1910.1200) is a hazardous substance subject to this chapter".

- Until 2012, the federal Hazard Communication Standard (HCS) incorporated TLVs as a definitive source for establishing that a chemical is hazardous.

In March 2012, the federal HCS was amended to remove reference to ACGIH TLVs as a mandatory basis for establishing that chemicals are hazardous. Consequently, a TLV based on reproductive or developmental toxicity no longer provides the basis for listing a chemical as known to the state to cause reproductive toxicity under Propostion 65.

[3] Health and Safety Code section 25249.8(a)

Table 1. Chemicals under Reconsideration for Listing as Known to Cause Reproductive Toxicity Based on the Labor Code Mechanism

Chemical	CAS Number	Basis for TLV
Hexafluoroacetone	684-16-2	Male reproductive toxicity ("testicular damage")
Phenylphosphine[a]	638-21-1	Male reproductive toxicity ("testicular damage")

[a] The Proposition 65 reproductive toxicity listing for phenylphosphine incorrectly specifies the endpoint as developmental, rather than male reproductive toxicity.

Reason for Reconsideration of Listing: Authoritative Bodies Chemical

Chlorsulfuron no longer meets the criteria for inclusion on the list on the basis of the Authoritative Bodies mechanism. This chemical is being presented to the DARTIC for a decision as to whether it has been clearly shown through scientifically valid testing according to generally accepted accepted principles to cause reproductive toxicity. If the Committee makes that determination, the chemical will remain on the list. Conversely, if the Committee determines the chemical has not been clearly shown to cause reproductive toxicity, the chemical will be delisted.

Table 2. Chemical under Reconsideration for Listing as Known to Cause Reproductive Toxicity Based on the Authoritative Bodies Mechanism

Chemical	CAS Number	Reproductive Toxicity Endpoints	Authoritative Body
Chlorsulfuron	6490-27-23	Developmental toxicity Female reproductive toxicity	U.S. EPA[a]

[a] Title 27, Cal. Code of Regs., section 25306(l)(4).

- Proposition 65 provides that "[a] chemical is known to the state to cause … reproductive toxicity within the meaning of this chapter if … a body considered to

be authoritative by [the state's qualified] experts has formally identified it as causing … reproductive toxicity"[4].

The U.S. Envirionmental Protection Agency (U.S. EPA) is an authoritative body for purposes of listing chemicals under Proposition 65. In 1994, U.S. EPA concluded that: "…there is sufficient evidence for listing chlorsulfuron on EPCRA [federal Emergency Planning and Community Right-to-Know Act, also known as the Toxic Release Inventory] section 313 pursuant to EPCRA section 313(d)(2)(B) based on the available developmental and reproductive toxicity data for this chemical."[5]

U.S. EPA was subsequently petitioned to remove chlorsulfuron from the list of chemicals subject to reporting under EPCRA section 313. On November 18, 2013, U.S. EPA stated that "[b]ased on U.S. EPA's review of the available data, there is no compelling evidence of the acute toxicity, carcinogenicity, reproductive or developmental toxicity, mutagenicity, or other serious chronic toxicity of chlorsulfuron".[6] (U.S. EPA determined that chlorsulfuron should remain subject to reporting under EPCRA section 313 based on its conclusion that chlorsulfuron can reasonably be anticipated to cause toxicity to aquatic plants.)

The regulations for authoritative bodies listing state that:

- "Subsequent to the addition of a chemical determined to have been formally identified by an authoritative body as causing cancer or reproductive toxicity to the list of chemicals known to the state to cause cancer or reproductive toxicity, the lead agency shall reconsider its determination that the chemical has been formally identified as causing cancer or reproductive toxicity if the lead agency finds:

  (1) there is no substantial evidence that the criteria identified in subsection (e) or subsection (g) have been satisfied, or

[4] Health and Safety Code section 25249.8(b)
[5] US Environmental Protection Agency (US EPA, 1994). Proposed Rule: Addition of Certain Chemicals; Toxic Chemical Release Reporting; Community Right to Know. *Federal Register* **59**: 1788.
US Environmental Protection Agency (US EPA, 1994). Final Rule: Addition of Certain Chemicals; Toxic Chemical Release Reporting; Community Right to Know. *Federal Register* **59**(229): 61432.
[6] US Environmental Protection Agency (US EPA, 2013). Chlorsulfuron: Community Right-to-Know Toxic Chemical Release Reporting. *Federal Register* **78(**236): 73791.

(2) the chemical is no longer identified as causing cancer or reproductive toxicity by the authoritative body.

"Reconsideration may be initiated by the lead agency on its own motion, or on a request from an interested party, including any member of the appropriate Committee. The lead agency shall refer chemicals under reconsideration pursuant to this subsection to the appropriate Committee for a recommendation concerning whether the chemical should continue to be included on the list of chemicals known to the state to cause cancer or reproductive toxicity. Pending such reconsideration, the chemical shall remain on the list." [7]

The statement by U.S. EPA cited above[8] establishes that the authoritative body no longer identifies chlorsulfuron as causing reproductive toxicity.

Reconsideration Procedure

These three chemicals are being brought to the DARTIC because they do not meet the criteria for inclusion on the list by any of the administrative listing mechanisms contained in the statute.

The Office of Environmental Health Hazard Assessment (OEHHA) has, through a contract with the Sheldon Margen Public Health Library at the University of California, Berkeley, conducted literature searches to identify studies that potentially provide information on the reproductive toxicity of each of these chemicals. The searches covered the three major reproductive toxicity endpoints, namely developmental toxicity and male and female reproductive toxicity. The databases that were searched and parameters used in these searches are described in Appendix A.

OEHHA staff reviewed the results of these searches and identified all studies that provided data on reproductive toxicity. Relevant studies were identified for all of the chemicals. For chlorsulfuron, regulatory studies submitted to U.S. EPA were identified but there were no studies in the open literature that provided relevant information. For each chemical, the design parameters and results of these studies on male reproductive, female reproductive and developmental toxicity are summarized in a table.

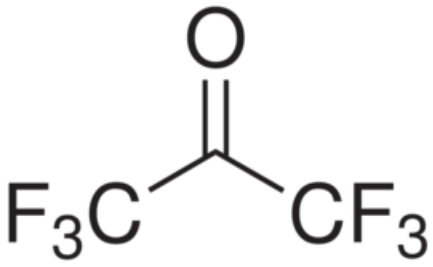
[7] Title 27, Cal. Code of Regs., section 25306(j)
[8] US Environmental Protection Agency (US EPA, 2013). Chlorsulfuron: Community Right-to-Know Toxic Chemical Release Reporting. *Federal Register* **78(**236):.73791.

The complete study reports for these chemicals have been provided to the DARTIC. These materials are available to the public upon request.

For completeness, the original ACGIH documents supporting development of the TLVs for the two ACGIH 'Labor Code' chemicals have also been provided to the DARTIC on CD. These documents were not used in the process that resulted in the listing under Proposition 65 of the chemicals identified in Table 1. Rather, identification of a TLV based in whole or in part on a reproductive toxicity endpoint in the document "Threshold Limit Values for Chemical Substances and Physical Agents in the Environment, American Conference of Governmental Industrial Hygienists (ACGIH)" (latest edition) resulted in the listing. Relevant entries from that document also have been provided on CD to the committee.

Labor Code Chemicals

Hexafluoroacetone



Molecular Formula: C_2F_6O

Hexafluoroacetrone is used as a chemical intermediate for hexafluoroisopropanol, polyacrylates used for textile coating, polyester coating for textiles, as a solvent for acetyl resins and polyamides, and as a polymer adhesive.

Relevant Studies

References on developmental toxicity:

Becci, P.J., Knickerbocker, M.J., Reagan, E.L., Parent, R.A. and L.W. Burnett (1982) Teratogenicity study of N-Methylpyrrolidone after dermal application to Sprague-Dawley rats. Fundamental and Applied Toxicology, **2**: 73-76.

Brittelli, M.R., Kulick, R., Dashiell, O. L., and W. E. Fayerweather (1979) Skin absorption of hexafluoacetone: teratogenic and lethal effects in the rat fetus. Toxicology and Applied Pharmacology, **47**:35-39.

Haskell Laboratory, E.I. Dupont de Nemours & Co. Inc. (1988) Pilot Developmental Toxicity Study of Hexafluoroacetone in the Rat Summary of Reproductive Outcome with Attached Letter and Receipt dated April 14, 1988 and Cover Letter dated 12/29/88. Submitted to US EPA, 3/3/89 (FYI-OTS-0189-0662).

Hoechst Celanese Corporation. (1991) Initial submission: letter submitting information contained in enclosed statistical analysis of a teratologic study of hexafluoacetone in rats. Submitted to US EPA, 11/21/91 (8EHQ-1191-1521).

References on male reproductive toxicity:

Gillies, P. J. and K. P. Lee (1983). "Effects of hexafluoroacetone on testicular morphology and lipid metabolism in the rat." Toxicology and Applied Pharmacology **68**(2): 188-197.

Gillies, P. J. and K. P. Lee (1985). "Effects of hexafluoroacetone on Leydig cell steroidogenesis and spermatogenesis in the rat." Exp Mol Pathol **42**(3): 353-365.

Lee, K. P. and P. J. Gillies (1984). "Ultrastructural alterations in hexafluoroacetone-induced testicular atrophy in the rat." Exp Mol Pathol **40**(1): 29-37.

Lee, K. P. and G. L. Kennedy, Jr. (1991). "Testicular toxicity of rats exposed to hexafluoroacetone (HFA) for 90 days." Toxicology **67**(3): 249-265.

Hexafluoroacetone (HFA)

Reference	Experimental Parameters					Endpoints Assessed	Results (Effects/NOEL/LOEL)		Comments
	Chemical (Source/ Purity/ Preparation)	Animal Model (Species/ Strain/Sex/ Age) N	Study Design	Exposure (Route/ Period/ Frequency/ Vehicle)	Doses or Concen-trations		Parents	Offspring	
Becci et al. 1982	Hexafluoroacetone (HFA) sesqui-hydrate (lot no. 021157), obtained from Aldrich Chemical Company, Inc., Milwaukee, Wisconsin, as a pure (100%) liquid. Prepared fresh daily as a 25% solution in water for application.	Young adult Sprague-Dawley rats mated in house, caged for mating 1:1 male:female Range finding study: N=5 pregnant females/group Teratology study: N= 25 pregnant females/group	Range-finding and teratology study components. Dams sacrificed on GD20.	Dermal application to skin, 25 cm^2 clipped free of fur, GD 6-15, applied daily (both study components). Animals fitted with collars to prevent licking. Vehicle: tap water	Range finding: 0, 5 mg/kg body wt/day (See Comments) Teratology: 0 (tap water), 10 mg/kg body wt/day	Standard teratological evaluation. Daily observations of maternal animals for "general appearance, behavior, and mortality." Urogenital tracts of all females were examined at sacrifice on day 20.	Range finding: 4/5 treated ♀s pregnant. Body weight gain in treated dams did not differ from controls. Teratology: 24/25 ♀s pregnant. Body weight gain in treated dams did not differ from water controls.	Range finding: No significant difference from controls for: mean number of viable offspring/dam, mean implantations/dam, mean resorptions/dam, or mean fetal weight. Teratology: No significant difference from water controls for: mean number of viable offspring/dam, sex ratio, implantation frequency, or frequency of soft tissue anomalies. ↑ Mean resorptions/dam ($p \leq 0.05$) ↓ Fetal weight ($p \leq 0.05$) ↑ Skeletal anomalies ($p \leq 0.05$)	Hexafluoro-acetone used as positive control for dermal teratogenicity.

Hexafluoroacetone (HFA) (continued)

Reference	Experimental Parameters					Endpoints Assessed	Results (Effects/NOEL/LOEL)		Comments
	Chemical (Source/ Purity/ Preparation)	Animal Model (Species/ Strain/Sex/ Age) N	Study Design	Exposure (Route/ Period/ Frequency/ Vehicle)	Doses or Concen-trations		Parents	Offspring	
Brittelli et al. 1979	Hexafluoroace-tone (HFA) trihydrate, obtained from Allied Chemical Company as a pure (100%) liquid (sp gr 1.60 g/ml). 5 % stock solution prepared in water, and dilutions for application prepared fresh daily with water.	Primigravida ChR-CD albino rats from Charles River Breeding Laboratories; sperm-positive vaginal smear = GD1 Range finding study: N=15 pregnant rats total Teratology study: N=14/ exposed group N=15 controls	Range-finding and teratology study components. Dams sacrificed on GD21 for standard teratological evaluation of uterine contents.	Dermal application to shaved skin of back (rubbed in to discourage oral intake from licking) on GD 6-16, applied daily (both study components). Vehicle: water	Range finding: 10 doses ranging from 2.3 to 90 mg/kg/day. Teratology study: 0 (water), 1, 5, 25 mg/kg/day	Standard teratological evaluation. Pregnant females were observed daily during treatment, and weighed on GD 1, 6-16, 20, and 21. .	Range finding: At 90 mg/kg/day maternal toxicity was observed (perineal staining and weight loss). Teratology study: 25% of treated animals (all doses): slight dermal irritation. No significant differences among groups for pregnancy rate. ↓ final maternal weight at 5 and 25 mg/kg/day ($p \leq 0.05$).	Range finding: At 40 mg/kg/day and above, all but one of the fetuses was resorbed early. Litters with live fetuses had high percentage of abnormalities. Teratology study: 25 mg/kg/day: ↓ Live fetuses/litter ↓ Mean fetal weight and crown rump length ↑ Resorptions and dead fetuses ↑ Resorptions/litters with resorptions ↑ Frequency of litters with pale fetuses, hemorrhages. anasarca, anopthalmia, hydronephrosis, cleft palate, hydrocephalus, small kidneys, wavy ribs, bipartite vertebral centra, unossified carpals and/or tarsals, scoliosis, and chonrodystrophy. 5 mg/kg/day: ↑ Frequency of litters with stunted fetuses, pale fetuses, hemorrhage, hematoma, wavy ribs, and bipartite vertebral centra. 1 mg/kg/day: ↑ Frequency of litters with hydronephrosis ($p < 0.05$ for each effect listed here)	

Hexafluoroacetone (HFA) (continued)

Reference	Experimental Parameters					Endpoints Assessed	Results (Effects/NOEL/LOEL)		Comments
	Chemical (Source/ Purity/ Preparation)	Animal Model (Species/ Strain/Sex/ Age) N	Study Design	Exposure (Route/ Period/ Frequency/ Vehicle)	Doses or Concen-trations		Parents	Offspring	
Haskell Laboratory 1988	Hexafluoroacetone (HFA) Source/purity not stated	Pregnant female rats, strain and source not stated. N = 6/group	Pilot, range-finding developmental toxicity study Dams sacrificed on GD 22	Inhalation: 6 hr/day, on GD 7-16.	0 (air), 0.1, 10, 30, or 60 ppm	Fetuses weighed, counted, and examined for externally-visible malformations	Mortality: 6/6 dams exposed to 60 ppm sacrificed *in extremis* after two days exposure. 4/6 dams found dead after exposure to 30 ppm. Dams exposed to lower concentrations survived. No clinical symptoms or body weight effects observed in surviving dams or at lower concentrations.	The 2 surviving dams at 30 ppm had completely resorbed litters. 4/6 litters exposed to 10 ppm completely resorbed. The 2 remaining litters at 10 ppm had only 3 live fetuses between them. 2 of these fetuses were described as malformed, the third as having "a developmental variation." No malformations observed at 0.1 ppm. Mean fetal weight and resorption frequency were not affected at this concentration.	Abbreviated reports. More detail available on the pilot study.

Hexafluoroacetone (HFA) (continued)

Reference	Experimental Parameters					Endpoints Assessed	Results (Effects/NOEL/LOEL)		Comments
	Chemical (Source/ Purity/ Preparation)	Animal Model (Species/ Strain/Sex/ Age) N	Study Design	Exposure (Route/ Period/ Frequency / Vehicle)	Doses or Concen-trations		Parents	Offspring	
Haskell Laboratory 1988 (continued)	Hexafluoro-acetone (HFA) Source/purity not stated	As above. N = 24/group	Full developmental toxicity study Dams sacrificed on GD 22	Inhalation exposure as above on GD 7-16	0 (air), 0.1, 1, 7 ppm	Maternal body weight, food consumption, and clinical signs were measured throughout. Maternal gross necropsy findings and liver weights recorded at sacrifice. Standard teratological evaluation	No significant effects on maternal body weight or food consumption. Maternal body weight gain comparable in all groups during exposure. Post-exposure until sacrifice, maternal body weight gain was lower in the high (7 ppm) concentration group than in controls. This was considered attributable to lower fetal weights, since adjusted maternal weights at sacrifice were comparable among all groups. No clinical symptoms attributed to HFA exposure The only postmortem HFA-related maternal finding was an increase in absolute and relative liver weight at both the intermediate (1 ppm) and high (7 ppm) concentrations.	↓ Mean litter size at 7 ppm (significance level unknown) ↑ Number and percentage of total resorptions and late resorptions at 7 ppm ↑ late resorptions at 1 ppm. ↓ Mean total and male and female fetal weights at 1 and 7 ppm. ↓ Weight of female fetuses at 0.1 ppm. The lower weight of the female fetuses was considered a minimal effect; being just below the low end of the range of historical control data from this laboratory for female fetuses. ↑ Total malformations at 7 ppm, primarily due to a large number of fetuses with anasarca and/or cleft soft palates. ↑ percentage of litters with developmental variations at both 1 and 7 ppm, primarily due to skeletal variations. ↑variations due to retarded development (partial ossifications) at 7 ppm.	The full study is described in a 2-page letter that refers to a full study report that was to be prepared. The full report could not be identified by OEHHA.

Hexafluoroacetone (HFA) (continued)

Reference	Experimental Parameters					Endpoints Assessed	Results (Effects/NOEL/LOEL)		Comments
	Chemical (Source/ Purity/ Preparation)	Animal Model (Species/ Strain/Sex/ Age) N	Study Design	Exposure (Route/ Period/ Frequency/ Vehicle)	Doses or Concen-trations		Parents	Offspring	
Hoechst 1991	Hexafluoroacetone (HFA) Source/purity not stated	Pregnant female rats, strain not stated. N = 15 controls N = 14/exposed group	Teratology study Dams sacrificed on GD 21.	Dermal application daily on GD 6-16.	0, 1, 5, 25 mg/kg/day.	Results of a standard teratological evaluation reported, but no description of examination protocol provided. No description of assessment or evaluation of maternal systemic parameters provided.	↓ Final body weight at 5 and 25 mg/kg/day	No significant differences among groups in the numbers or percentages of bred females pregnant at sacrifice. Significance determined at the 0.05 level of probability compared to concurrent controls. 25 mg/kg/day only group affected: ↑ Litters with resorptions, litters with dead fetuses, resorptions/litters with resorptions. ↓ Live fetuses per litter, fetal weight, and fetal crown rump length. ↑ Hematoma, pale fetuses, hemorrhages, wavy ribs, and vertebral bipartite center at 5 and 25 mg/kg/day. ↑ Anasarca, anopthalmia, cleft palate, hydrocephalus, small kidney, scoliosis, unossified carpals and tarsals, and chondrodystrophy at 25 mg/kg/day ↑ Litters with small, stunted fetuses at 5 mg/kg/day ↑ Litters with hydronephrosis at 1 and 25 mg/kg/day.	Document is a letter containing summary tables of data and information about statistical analysis. Malformations data were compared to historical data from Charles River for the years 1966 through 1968. Those comparisons have not been included here as the source of the rats used in this study appears to have been in-house, and it appears to have been conducted at a later date (date on report indicates 1977).

Hexafluoroacetone (HFA) (continued)

Reference	Experimental Parameters					Endpoints Assessed	Results (Effects/NOEL/LOEL)		Comments
	Chemical (Source/ Purity/ Preparation)	Animal Model (Species/ Strain/Sex/ Age) N	Study Design	Exposure (Route/ Period/ Frequency/ Vehicle)	Doses or Concen-trations		Systemic Toxicity	Reproductive Toxicity	
Gillies and Lee 1983	Hexafluoroacetone (HFA) sesquihydrate DuPont, purity 100%	Male CRL: CD rats, mean weight 234 g. N = 8/group.	Male reproductive toxicity study: sperm parameters and testicular pathology Sacrifice at 24 hours after last dose.	Dermal application in a volume of 200 µl to a shaved area on the back, daily for 14 days. Vehicle: water	0 (water), 13, 39, 130 mg/kg/day	Right testis from each rat fixed and stained for light microscopy. Left testis from each rat incubated with radiolabeled precursors, and processed for biochemical studies. No description of assessment or evaluation of systemic parameters provided.	130 mg/kg/day: Failed to gain weight, and "moderately severe chromodacryorrhea" 39 mg/kg/day: Gained ~ 3 g/day "mild chromodacryorrhea" 13 mg/kg/day: Gained ~ 4 g/day "No remarkable clinical signs."	"Moderate" testicular atrophy at 39 mg/kg/day, half of rats. "Severe" testicular atrophy at 130 mg/kg/day, all rats. Spermatids and spermatocytes were the most affected cell types. Spermatogonia and Sertoli cells appeared less vulnerable. ↑ triacylglycerol and phospholipid incorporation of radiolabeled glucose and acetate (at 39 and 130 mg/kg/day; $p \leq 0.05$) ↓ Sterol incorporation of radiolabeled acetate, ↑ Incorporation of radiolabeled glucose (both: 130 mg/g/day; $p \leq 0.05$). No effect on levels of vitamin A or zinc.	

Hexafluoroacetone (HFA) (continued)

Reference	Experimental Parameters					Endpoints Assessed	Results (Effects/NOEL/LOEL)		Comments
	Chemical (Source/ Purity/ Preparation)	Animal Model (Species/ Strain/Sex/ Age) N	Study Design	Exposure (Route/ Period/ Frequency/ Vehicle)	Doses or Concen-trations		Systemic Toxicity	Reproductive Toxicity	
Gillies and Lee 1985	Hexafluoroacetone (HFA) sesqui-hydrate DuPont, purity 100%	Male Crl: CD rats; mean weight of 240 g N = 7 exposed and N = 8 controls	Male reproductive toxicity study: Leydig cell-enriched fractions from treated and control rats were incubated with radiolabeled acetate and mevalonate. Control rats pair fed	Dermal application daily for 14 days. Vehicle: distilled water.	0 (distilled water), 130 mg/kg/day	Incorporation of radiolabel into nonsaponifiable lipids. Testicular testosterone levels. Luteinizing hormone, follicle-stimulating hormone, and testosterone blood levels were measured in treated and control rats after 1, 3, 7, and 14 days of treatment. Testicular histology.	Similar final body weight for treated and control (pair fed) groups	43% ↓ in testicular weights of treated compared to control (pair fed) rats ($p \leq 0.05$). Significant ($p \leq 0.05$) differences between treated and control groups for incorporation of radiolabeled acetate and mevalonate into nonsaponifiable lipids in Leydig cell-enriched testicular fractions. Histology showed degenerative changes in spermatocytes and other pathological effects as early as 1 day following the first dose of HFA. Effects became more severe as treatment proceeded. Luteinizing hormone and testosterone levels were not affected during HFA treatment. Follicle-stimulating hormone levels were elevated 48% after 14 days of treatment (no mention of statistics).	Refers to earlier metabolic studies showing HFA not metabolized, but distributed throughout tissues of the body.

Hexafluoroacetone (HFA) (continued)

Reference	Experimental Parameters					Endpoints Assessed	Results (Effects/NOEL/LOEL)		Comments
	Chemical (Source/ Purity/ Preparation)	Animal Model (Species/ Strain/Sex/ Age) N	Study Design	Exposure (Route/ Period/ Frequency/ Vehicle)	Doses or Concen-trations		Systemic Toxicity	Reproductive Toxicity	
Gillies and Lee 1985 (continued)	As above	Male Crl: CD rats	Testes from untreated rats were incubated *in vitro* with HFA.	Not applicable	1.0 mM	Testes from normal rats were decapsulated and incubated in the presence of 1.0 mM hexafluoroacetone and 10 pCi/ml of [^{14}C]acetate for 3 hr at 375°C. Leydig cell-enriched fractions were isolated from the seminiferous tubule-interstitial cell matrix and the nonsaponifiable lipids were extracted and analyzed as described above.	Not applicable	In vitro incubation of testes from unexposed rats with HFA did not affect steroidogenesis.	

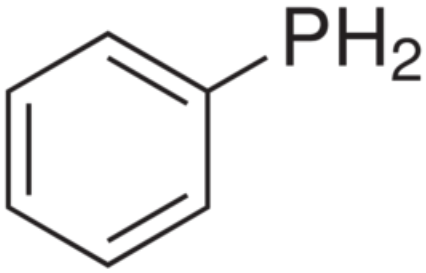
Hexafluoroacetone (HFA) (continued)

Reference	Experimental Parameters					Endpoints Assessed	Results (Effects/NOEL/LOEL)		Comments
	Chemical (Source/ Purity/ Preparation)	Animal Model (Species/ Strain/Sex/ Age) N	Study Design	Exposure (Route/ Period/ Frequency/ Vehicle)	Doses or Concen-trations		Systemic Toxicity	Reproductive Toxicity	
Lee and Gillies 1984	Hexafluoroacetone (HFA) sesquihydrate DuPont, purity >99%	Male Crl: CD rats; mean weight of 234 g N = 10/group	Male reproductive toxicity study: Gross and microscopic evaluation of testes. Control groups pair fed to treated groups. Sacrificed 24 hours following last dose for gross examination; testes removed and processed for light (all groups) or electron microscopy (high dose group only)	Dermal application in a volume of 200µl to a shaved area on the back daily for 14 days. Vehicle: water	0 (water), 13, 39, 130 mg/kg/day	Gross and histological examination of testes	Not discussed	Testicular atrophy at 39 (slight in 50% of rats) and 130 (severe in all rats) mg/kg/day Greatest effect on spermatids; lesser effect on spermatocytes; spermatogonia unaffected. ↑ Number of lipid droplets in Sertoli cells (not quantified) observed by electron microscopy of testes from high-dose rats. Leydig cells appeared normal by light microscopy; ultrastructural changes evident at the electron microscopy level (high dose group).	

Hexafluoroacetone (HFA) (continued)

Reference	Experimental Parameters					Endpoints Assessed	Results (Effects/NOEL/LOEL)		Comments
	Chemical (Source/ Purity/ Preparation)	Animal Model (Species/ Strain/Sex/ Age) N	Study Design	Exposure (Route/ Period/ Frequency/ Vehicle)	Doses or Concen-trations		Systemic Toxicity	Reproductive Toxicity	
Lee and Kennedy, Jr. 1991	Hexafluoro-acetone (HFA) DuPont, Purity 100%	Male Crl: CDBR rats; weights ranging from 245-327 g; N = 40/group	Male reproductive toxicity study: Testicular effects. Sacrifice after 30 or 90 days exposure, or 28 or 84 days following the end of exposure (post-exposure, PE).	Inhalation, 6 hr/day, 5 days/week for 90 days.	0 (air), 0.1, 1.0, 12 ppm	Daily observations for clinical signs. Food and water consumption "noted but not measured." All animals weighed weekly. At sacrifice, testes and epididymides were removed, weighed, and prepared for light microscopy. Testicular damage was quantified by grading the numbers of affected seminiferous tubules. Stage-specific spermatogenesis was evaluated by standard techniques.	30 and 90 days exposure; and 28 and 84 days PE at 12 ppm HFA: ↓ Body weight (all time points compared to control $p \leq 0.05$). Clinical signs: "occasional irregular respiration and purple discoloration of the toes in rats exposed to 12 ppm HFA."	30 and 90 days exposure; and 28 and 84 days PE at 12 ppm HFA: ↓ Absolute testes weight (all time points compared to control $p \leq 0.05$). 30 days exposure to 12 ppm HFA: Testicular atrophy Oligospermia or aspermia and epididymal tubules. Effects on spermatids and spermatocytes. 90 days exposure, 12 ppm HFA: Severe testicular atrophy Effects on almost all seminiferous tubules. Mature and immature spermatids disappeared from the seminiferous tubules. Epididymal tubules devoid of spermatozoa. 28 days PE, 12 ppm HFA: Regeneration evident but variable, and not restored to normality. 84 days PE, 12 ppm HFA: Spermatogenesis only partially restored to normality.	The methods section of the paper states that "A total of 160 male… rats… Were divided into four groups of 40 males and 40 females each." No further mention is made of female rats. May have been a typographical error, or data for females may have never been reported (did not appear in literature searches).

Phenylphosphine



Molecular Formula: C_6H_7P

Phenylphosphine is primarily used as a precursor in the manufacture of other organic phosphorus compounds.

Relevant Studies

Du Pont (1992). "Initial submission: 90-day inhalation toxicity study of phenylphosphine in rats and dogs with cover letter dated 101592." Submitted to U.S EPA EPA/OTS **920009737**: #88-920009737.

Waritz, R. S. and R. M. Brown (1975). "Acute and subacute inhalation toxicities of phosphine, phenylphosphine and triphenylphosphine." Am Ind Hygn Asscn J **36**(6): 452-458.

Phenylphosphine

Reference	Experimental Parameters					Endpoints Assessed	Results (Effects/NOEL/LOEL)		Comments
	Chemical (Source/ Purity/ Preparation)	Animal Model (Species/ Strain/Sex/ Age) N	Study Design	Exposure (Route/Period/ Frequency/ Vehicle)	Doses/ Concen-trations		Systemic Toxicity	Reproductive Toxicity	
Du Pont 1992	Test material synthesized as needed by Charles King, Textile Fibers Department, Experimental Station. Purity not stated	Rats Females, average initial body weight: 224 g Males, average initial body weight: 307 g N=20/sex/ group	90-day inhalation toxicity study. Interim sacrifices of 5 males & 5 females per group at test days 30 and 90, and after 28 days recovery. Remaining rats sacrificed after 65 days recovery.	Inhalation, 6 hr/day, 5 days/week, total 59 exposures	0 (air), 0.3, and 3.0 ppm (0, 0.6, 2.2 ppm average concentration per exposure)	Hematological evaluations: erythrocyte counts, hemoglobin concentration, hematocrit, and total leukocyte count. Performed prior to start of test, 4 times during treatment, and twice during recovery. 10 males & 10 females tested at each time point. Gross and histopathologic assessments at sacrifice. No other methods information was provided. Presumably body weights were measured, as results for body weights and growth rates were presented.	Severe clinical, hematological, and histopathologic effects at 2.2 ppm. ↓ growth rate after 30 days; ↓ bw after 60 days of treatment. Symptoms and growth rate returned to normal during recovery. Neurological effects (hypersensitivity to sound and touch) at both concentrations, with a concentration-response.	Irreversible, severe testicular degeneration seen at 2.2 ppm in 5/5 males at terminal sacrifice.	

Phenylphosphine (continued)

Reference	Experimental Parameters					Endpoints Assessed	Results (Effects/NOEL/LOEL)		Comments
	Chemical (Source/ Purity/ Preparation)	Animal Model (Species/ Strain/Sex/ Age) N	Study Design	Exposure (Route/Period/ Frequency/ Vehicle)	Doses/ Concen-trations		Systemic Toxicity	Reproductive Toxicity	
Du Pont 1992 (continued)	As above	Male Beagle dogs, average initial body weight: 10.7 kg N=4/group	90-day inhalation toxicity study. 2 dogs per group sacrificed at 90 days, and following 28 days of recovery.	As above	As above	Hematological evaluations as above. Performed 2X prior to treatment; after 1 month, 6 weeks, 2 months, and 3 months of treatment; 1 month after last exposure. 4 dogs tested at each time point.	At 0.6 ppm: appetite loss, nausea, lacrimation, diarrhea; all clearing during recovery. At 2.2 ppm: above more severe, plus ↑ water consumption. ↓ Hematological values at all time points tested. Evidence of moderate anemia at all time points after 1 month. No effect on growth.	Light, diffuse testicular degeneration at 2.2 ppm in 3/4 dogs; focal testicular degeneration in 1/4 dogs each in control and 0.6 ppm groups. Oligospermia in 2/4 dogs at 2.2 ppm, and in 1/4 dogs at 0.6 ppm.	Dogs distributed among test groups on the basis of size and weight, not pretreatment hematological results. 2 dogs in the 0.6 ppm group had low hemoglobin prior to treatment (other hematological endpoints normal)

Phenylphosphine (continued)

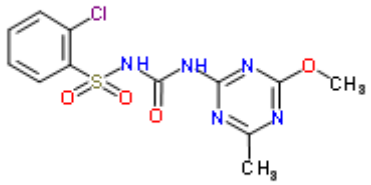
Reference	Experimental Parameters					Endpoints Assessed	Results (Effects/NOEL/LOEL)		Comments
	Chemical (Source/ Purity/ Preparation)	Animal Model (Species/ Strain/Sex/ Age) N	Study Design	Exposure (Route/Period/ Frequency/ Vehicle)	Doses/ Concen-trations		Systemic Toxicity	Reproductive Toxicity	
Waritz and Brown 1975	Synthesized by DuPont company Purity not stated	Male Charles River-CD rats (250-275 g) N=6/group	Acute exposure study. Rats were sacrificed and examined at various times after exposure. 2 rats sacrificed at each of 1, 2 and 7 days after 0.78 µM/liter (19 ppm); 2 sacrificed at 14 days after 1.81 µM/liter (44 ppm); 2 rats which died during exposure to 1.31 µM/liter (32 ppm) also examined No data on any other animals were reported	Inhalation 4 hours (one time)	0 ("nitrogen/ oxygen atmosphere"), 0.78 µM/ liter (19 ppm); 1.31 µM/liter (32 ppm) 1. 81 µM/liter (44 ppm)	Gross pathology; organ weights (including testis); organ histology (including testes and epididymis)	Clinical symptoms of respiratory irritation during exposure. No evidence of toxicity from tissues examined.	None	Not clearly stated, but spermatogenesis apparently assessed histopathologically The same group of six control rats used in both the acute and the subacute parts of the study.

Phenylphosphine (continued)

Reference	Experimental Parameters					Endpoints Assessed	Results (Effects/NOEL/LOEL)		Comments
	Chemical (Source/ Purity/ Preparation)	Animal Model (Species/ Strain/Sex/ Age) N	Study Design	Exposure (Route/Period/ Frequency/ Vehicle)	Doses/ Concen-trations		Systemic Toxicity	Reproductive Toxicity	
Waritz and Brown 1975 (continued)	As above	As above	Subacute exposure study. 3 control and 3 exposed rats sacrificed immediately following end of treatment; remaining animals sacrificed 14 days following the end of treatment. Treatment concentration ~ 1/5 LC_{50} as calculated from the acute experiment.	Inhalation, 4 hours/day for 10 days	0 or average concentration during treatment of 0.31 µM/liter.	As above	Symptoms of respiratory irritation during exposure, similar to acute exposure study. Dermatitis around mouth and feet (appeared after last exposure, cleared within 5 days). Foci of red blood cell formation in the spleen, still evident 14 days after exposure ceased. ↓ wt gain during 10-day treatment; returned to normal 14-day after exposure ceased.	Mild depression of spermatogensis observed in two of three exposed rats immediately after the last exposure, and in 1/3 rats 14 days after the last exposure.	As above

Authoritative Body Chemical

Chlorsulfuron



Molecular Formula: $C_{12}H_{12}ClN_5S$

Chlorsulfuron is used as a pre- and post-emergent herbicide to control a variety of weeds on cereal grains, pasture and rangeland, industrial sites, and turf grass.

Relevant Studies

Alvarez L. (1991a). Teratogenicity Study of DPX-W4189-165 (Chlorsulfuron) in Rabbits. E.I.du Pont de Nemours and Company. Laboratory Project ID 306-90. Haskell Laboratory for Toxicology and Industrial Medicine, Newark, DE 19714. USA.

Mylchreest, E. (2005a) Supplement 1 to Alvarez L. (1991a). Teratogenicity Study of DPX-W4189-165 (Chlorsulfuron) in Rabbits. E. I. du Pont de Nemours and Company. Laboratory Project ID 306-90. Haskell Laboratory for Health and Environmental Sciences, Newark, DE 19714. USA.

Lewis, J.M. (2008) Supplement 2 to Alvarez L. (1991a). Teratogenicity Study of DPX-W4189-165 (Chlorsulfuron) in Rabbits. E.I.du Pont de Nemours and Company. Laboratory Project ID 306-90. Haskell Laboratory for Toxicology and Industrial Medicine, Newark, DE 19714. USA.

Munley, S.M. (2012a) Supplement 3 to Alvarez L. (1991a). Teratogenicity Study of DPX-W4189-165 (Chlorsulfuron) in Rabbits. E.I.du Pont de Nemours and Company. Laboratory Project ID 306-90. Haskell Laboratory for Toxicology and Industrial Medicine, Newark, DE 19714. USA.

Alvarez L. (1991b). Teratogenicity Study of DPX-W4189-165 (Chlorsulfuron) in Rats. E.I.du Pont de Nemours and Company. Laboratory Project ID 734-90. Haskell Laboratory for Toxicology and Industrial Medicine, Newark, DE 19714. USA.

Hoberman, A. (1980). Chlorsulfuron (DPX-W4189) Technical: Teratology Study in Rabbits. E.I.du Pont de Nemours and Company. HLO 534-80, Laboratory Project ID 201-536. Haskell Laboratory for Toxicology and Industrial Medicine, Newark, DE 19714. USA.

Hoberman, A. (2010) Supplement 1 to Hoberman, A. (1980). Chlorsulfuron (DPX-W4189) Technical: Teratology Study in Rabbits. E.I.du Pont de Nemours and Company. HLO 534-80, Laboratory Project ID 201-536. Haskell Laboratory for Toxicology and Industrial Medicine, Newark, DE 19714. USA.

Hoberman, A. (2011) Supplement 1, Revision 1 to Hoberman, A. (1980). Chlorsulfuron (DPX-W4189) Technical: Teratology Study in Rabbits. E.I.du Pont de Nemours and Company. HLO 534-80, Laboratory Project ID 201-536. Haskell Laboratory for Toxicology and Industrial Medicine, Newark, DE 19714. USA.

Munley, S. M. (2014) Supplement 1, Revision 2 to Hoberman, A. (1980). Chlorsulfuron (DPX-W4189) Technical: Teratology Study in Rabbits. E.I.du Pont de Nemours and Company. HLO 534-80, Laboratory Project ID 201-536. Haskell Laboratory for Toxicology and Industrial Medicine, Newark, DE 19714. USA.

Mylchreest, E. (2005b) Chlorsulfuron (DPX-W4189) Technical: Multigeneration Reproduction Study in Rats. Laboratory Project ID: DuPont-13475. E.I. du Pont de Nemours and Company, Wilmington, Delaware 19898, U. S. A.

Wood, C.K. (1981). Long-Term Feeding Study with 2-Chloro-N-[(4-methoxy-6-methyl-1,3,5-triazin-2-yl) aminocarbonyl] benzenesulfonamide (INW-4189) in Rats. E.I.du Pont de Nemours and Company. Laboratory Project ID 557-81. Haskell Laboratory for Toxicology and Industrial Medicine, Newark, DE 19714. USA.

Munley, S. M. (2011) Supplement 3, Revision 1 to Wood, C.K. (1981). Long-Term Feeding Study with 2-Chloro-N-[(4-methoxy-6-methyl-1,3,5-triazin-2-yl) aminocarbonyl] benzenesulfonamide (INW-4189) in Rats. E.I.du Pont de Nemours and Company. Laboratory Project ID 557-81. Haskell Laboratory for Toxicology and Industrial Medicine, Newark, DE 19714. USA.

Munley, S. M. (2012b) Supplement 3, Revision 2 to Wood, C.K. (1981). Long-Term Feeding Study with 2-Chloro-N-[(4-methoxy-6-methyl-1,3,5-triazin-2-yl) aminocarbonyl] benzenesulfonamide (INW-4189) in Rats. E.I.du Pont de Nemours and Company. Laboratory Project ID 557-81. Haskell Laboratory for Toxicology and Industrial Medicine, Newark, DE 19714. USA.

Chlorsulfuron

Reference	Experimental Parameters					Endpoints Assessed	Results (Effects/NOEL/LOEL)		Comments
	Chemical (Source/ Purity/ Preparation)	Animal Model (Species/ Strain/Sex/ Age) N	Study Design	Exposure (Route/Period/ Frequency/ Vehicle)	Doses/ Concen-trations		Parents	Offspring	
Hoberman 1980 (Haskell Laboratory)	Haskell #12,700 (an off-white powder from E.I. du Pont de Nemours & Co., Inc. (Haskell Laboratory)) (purity not specified by author but reported by CA Department of Pesticide Regulation to be 94%)	Pregnant New Zealand White Rabbits N=66 Group 1: controls, 16 rabbits Group 2: low dose, 16 rabbits Group 3: mid dose, 17 rabbits Group 4: high dose, 17 rabbits	Teratology study	Oral intubation GD 6-19 Vehicle: corn oil	0 (vehicle), 10, 25, 75 mg/kg-d	Maternal body weight change, food consumption, clinical observations, survival, gross pathology, implantation efficiency, offspring viability, and development	Reduced maternal body weight gain in treated groups during GD 6-19 Reported NOEL = 25 mg/kg-d	Increased resorptions and decreased fetal viability reported at all dose levels (Reported to be significant at 75 mg/kg-d, p value not provided) Group mean resorptions of 11.6, 23.9, 13.8, and 31.3% per litter at 0, 10, 25, and 75 mg/kg-d, respectively.	
Hoberman 2010 (Haskell Laboratory) Supplement 1 to Hoberman, 1980	Supplemental analysis of data from Hoberman (1980), reviewing fetal resorption data. States that single conceptus litters are known to be an insufficient number of implantations to support pregnancy in New Zealand White Rabbits [original study data show 3 pregnancies at 25 mg/kg and 1 at 75 mg/kg with one implantation – 1 pregnancy at each dose level resulted in resorption of the conceptus, and 2 pregnancies at 25 mg/kg each produced a live fetus]. When data from totally resorbed litters were excluded (0 in the control and one each in each of the 3 dose groups) group mean resorptions were 11.6, 17.3, 9.7, and 14.8% per litter at 0, 10, 25, and 75 mg/kg-d, respectively [resorbed litter in the 10 mg/kg group had 4 implantations]. The author considered the historical control database and the author's recalculated resorption rates (excluding resorbed litters), and concluded that dosages of chlorsulfuron as high as 75 mg/kg-d when administered during the period of major organogenesis did not produce developmental toxicity (embryo/fetal toxicity or teratogenicity).								

Hoberman 2011 (Haskell Laboratory) Supplement 1, Revision 1 to Hoberman, 1980	This revision of supplement 1 was done after a calculation error was discovered after the supplement was issued. (In the original supplement, the mean percent resorptions per litter was calculated two ways, either including or excluding the litters with total resorptions in the calculations. The authors considered that the decision of whether to include or exclude totally resorbed litters in the calculations to derive group means for numbers of resorptions per litter or percent resorptions per litter is a consideration that is best made on a case-by-case basis in the context of the entire set of data from a study.) The purpose of Revision 1 of supplement 1 is to provide all data as individual animal data, to correct a calculation error, and to present group means that both include and exclude animals with total resorptions. Hoberman 2011 questioned the fetal resorption data in the Hoberman 1980 study. First, increased fetal resorptions were not seen in a subsequent study (Alvarez 1991b) which tested doses up to 1000 mg/kg/day. Second, several of the totally resorbed litters in Hoberman 1980 were quite small and very small litters are often less likely to be sustained given the diminished production of hormones needed to sustain pregnancy. Third, in the current and subsequent developmental toxicity studies in rabbits, there was no other evidence of corroborative developmental toxicity. Therefore, the case was made that exclusion of the totally resorbed litters was warranted and the erroneous calculation yielded a mean value at 75 mg/kg/day that was much closer to that reported for the concurrent control group. The resorption incidence data were similar to background levels, lacked dose dependency, and were not reproducible even at doses of up to 1000 mg/kg/day which warranted reconsideration of the findings from the 1980 study in which there was no other evidence of developmental toxicity. The author stated the weight of evidence justified a revision of the conclusion to reflect that dosages of chlorsulfuron as high as 75 mg/kg/day when administered during the period of major organogenesis did not produce any developmental toxicity (embryo/fetal toxicity or teratatogenicity).
Munley 2014 (Haskell Laboratory) Supplement 1, Revision 2 to Hoberman, 1980	This second revision of supplement 1 was done to correct calculations and table entries; also, a literature reference was added to the first paragraph of the following section, “Reason for Revision 1”. The corrected calculations resulted from consideration of whether data from selected females should be excluded from the calculations. In Revision 2, data from the female that was found dead on gestation day 18 have been appropriately excluded from all litter mean calculations. The second set of calculations that have been corrected pertain to data from two females in group 4 which were erroneously included previously. For the first female, it was noted at study termination that uterine scars were present which were indicative of pregnancy at some prior time. Since the timing of the prior pregnancy and the identification of any uterine contents is unknown, data from this female should be excluded from all litter mean calculations. For the second female, data from this animal that was euthanized following clinical observations suggestive of abortion recorded on gestation day 28 have been appropriately excluded. The conclusion of Supplement 1, Revision 2 was the same as that of Supplement 1, Revision 1.

Chlorsulfuron (continued)

Reference	Experimental Parameters					Endpoints Assessed	Results (Effects/NOEL/LOEL)		Comments
	Chemical (Source/ Purity/ Preparation)	Animal Model (Species/ Strain/Sex/ Age) N	Study Design	Exposure (Route/Period/ Frequency/ Vehicle)	Doses/ Concen-trations		Parents	Offspring	
Alvarez 1991a (Haskell Laboratory)	Chlorosulfuron DuPont Crop Protection 98.2% purity	Main Study Inseminated, New Zealand White Rabbits 5 - 5.5 months old N=20 per group Total N = 100	Teratogenicity study	Gavage, once a day GD 7-19 Vehicle:aqueous 0.5% methyl cellulose (w/v) solution	0 (vehicle), 25, 75, 200, 400 mg/kg-d	Body weights, clinical signs, feed consumption, incidence of pregnancy, litter and fetal parameters, and malformations	Reported that no maternal toxicity was evident	Reported that no fetal toxicity was evident .	
		Supplemental Study Inseminated, New Zealand White Rabbits 5 - 5.5 months old N=20 per group Total N=60	As above	As above	0 (vehicle), 400, 1000 mg/kg-d	As above	Decreased maternal body weight gain on days 7-29 at 400 mg/kg-d Maternal toxicity at the highest dose (significant incidence of mortality, reduced body weight gain and increased clinical signs at 1000 mg/kg-d)	Reduced fetal weights at 400 mg/kg Fetal malformations (double aorta, ventricular septal defect and absent gallbladder) were seen at low frequency at 400 mg/kg-d. Minor fetal skeletal defects (hemivertebra malformations) at 400 mg/kg-d. Number of dams that aborted was significantly higher in the 1000 mg/kg-d group compared with controls. Decreased sternebra ossification at 1000 mg/kg-d	

Mylchreest 2005a (Haskell Laboratory) Supplement 1 to Alvarez 1991a (Volume 4 of Alvarez 1991a)	This supplement to the Alvarez 1991a study report was conducted to add one row of information (percent resorptions per litter) to the reproductive outcome tables for the main study and the supplemental study. For the main study, the percent resorptions per litter were 2.5, 10.5, 8.8, 9.6, and 5.6 for the control, 25, 75, 200, and 400 mg/kg-d dose groups, respectively. For the supplemental study, the percent resorptions per litter were 9.6, 4.1, and 9.4 for the control, 400, and 1000 mg/kg-d dose groups, respectively.
Lewis 2008 (Haskell Laboratory) Supplement 2 to Alvarez 1991a	Retabulation of data and retrospective statistical analysis of maternal and developmental findings from Alvarez (1991a). Lewis re-evaluated the findings of skeletal variation, partially ossified sternebrae from the main study [incidence reported as 13(6/16), 5(4/17), 10(7/15), 7(4/16), 13(5/16) fetuses (litters affected/total) at 0, 25, 75, 200, and 400 mg/kg/day, respectively] and the supplemental study [incidence reported as 5(1/10), 12(5/13), and 4(2/4) fetuses (litters affected/total) at 0, 400, and 1000 mg/kg/day, respectively], as reported by Alvarez 1991a. The author stated the incidences from all treated groups were low and not statistically different from the concurrent controls. In addition, Lewis reevaluated these findings of skeletal variation and other maternal and developmental findings in the context of historical control data (1983-1994) from multiple studies conducted in the same testing laboratory. Lewis did not consider these results to be test substance-related. The skeletal variations unossified sternebrae and/or partially ossified skull were observed in some treatment groups, but not the concurrent control group.
Munley 2012a (Haskell Laboratory) Supplement 3 to Alvarez 1991a	Additional statistical analyses to support the interpretation of the fetal body weight data from the main and supplemental studies reported by Alvarez (1991a). Pairwise analysis indicated that the only group with a mean value that was significantly different from the control group was the 75 mg/kg/day group and only for females. There was no effect on males in either study or when data from both the main and supplemental studies were combined (Alvarez, 1991a). The original offspring data were tabulated for both males and females. The purpose of the analyses in this Supplement was to determine whether there were any treatment-related changes in male or female fetal weights. Alvarez (1991a) had classified two fetuses at 200 mg/kg/day and one fetus at 400 mg/kg-d as stunted; these animals were excluded in the fetal body weight analyses conducted by Alvarez (1991a), but they were included in the Munley (2012a) fetal body weight analysis. The inclusion of the weights from these fetuses had no significant impact on either the means or the outcome of the analysis. The ANCOVA performed by Munley (2012a) did not identify any test compound-related effects on fetal weight.

Chlorsulfuron (continued)

Reference	Experimental Parameters					Endpoints Assessed	Results (Effects/NOEL/LOEL)		Comments
	Chemical (Source/ Purity/ Preparation)	Animal Model (Species/ Strain/Sex/ Age) N	Study Design	Exposure (Route/Period/ Frequency/ Vehicle)	Doses/ Concen-trations		Parents	Offspring	
Alvarez 1991b (Haskell Laboratory)	Chlorsulfuron 98.2% purity	Crl:CD*BR rats 25 inseminated females/group	Teratogenicity study (Guideline developmental toxicity study)	Oral (gavage) GD 7-16 Vehicle 0.5% methyl cellulose (w/v) in distilled water	0, 55, 165, 500, 1500 mg/kg/day.	Clinical observations, body weights (maternal and fetal) and food consumption External, skeletal, visceral examination of fetuses	Increased vaginal discharge during treatment at 500 and 1500 mg/kg/day; reduced body weights and food consumption at 1500 mg/kg/day ($p \leq 0.05$). Reported Maternal NOEL = 165 mg/kg/day	Reduced fetal body weights at 1500 mg/kg/day ($p \leq 0.05$). No significant increase in malformations in exposed groups. Reported Developmental NOEL = 500 mg/kg/day	Although not statistically significant, less severe reductions in maternal body weight gain and fetal body weights were noted at 500 mg/kg/day

Chlorsulfuron (continued)

Reference	Experimental Parameters					Endpoints Assessed	Results (Effects/NOEL/LOEL)		Comments
	Chemical (Source/ Purity/ Preparation)	Animal Model (Species/ Strain/Sex/ Age) N	Study Design	Exposure (Route/Period/ Frequency/ Vehicle)	Doses/ Concentrations		Systemic Toxicity	Reproductive Toxicity	
Mylchreest 2005b	Chlorsulfuron (DPX-W4189) technical Purity 97.6%	Crl:CD® (SD)IGS BR rats 30/sex/group for P1 and F1	Guideline two-generation reproduction study 1 litter per generation	Oral (diet) Premating – about 70 days, during mating, gestation and through the study for the two generations	0, 100, 500, 2500, 7500 ppm <u>100 ppm:</u> M: 6.01 (P1); 9.11 (F1) mg/kg/day F: 6.53 to 12.62 (P1) mg/kg/day; 7.15 to 11.23 (F1) mg/kg/day <u>500 ppm</u> M:30.1 (P1); 45.9 (F1) mg/kg/day F:32.6 to 61.2 (P1) mg/kg/day; 35.5 to 62.9 (F1) mg/kg/day <u>2500 ppm</u> M: 151 (P1); 226 (F1) mg/kg/day F:165 to 328 (F0) mg/kg/day;180 to 312 (F1) mg/kg/day <u>7500 ppm</u> M: 456 (P1); 701 (F1) mg/kg/day F: 498 to 1040 (P1) mg/kg/day; 556 to 972 (F1) mg/kg/day	Parents: clinical signs, food consumption, mortality, sperm parameters, estrous cycle parameters, mating, fertility, gestation length, number of implantation sites, necropsy results, and histology. Pups: clinical signs, survival, weights, developmental landmarks, organ weights, and gross pathology.	Reduction in bodyweight and bodyweight gain at 7500 ppm. Reported Parental NOEL = 2500 ppm (151 to 226 mg/kg/day for males during premating and 165 to 261 mg/kg/day for females during premating and/or gestation) Parents As above	No adverse effects reported even at highest dose level. Reported Reproductive NOEL = 7500 ppm (456 to 701 mg/kg/day for males during premating and 498 to 810 mg/kg/day for females during premating and/or gestation). Offspring No adverse effects reported even at highest dose level. Pup NOEL = 7500 ppm	Dose levels estimated by authors for premating, gestation and lactation periods. The test substance-related effects on body weights and body weight gains were noted at ≥500 ppm; however, only effects observed in P1 males at 7500 ppm were statistically significant and considered adverse by authors where overall mean body weight gain (test days 0-105) at 7500 ppm was 11% lower than the control.

Chlorsulfuron (continued)

Reference	Experimental Parameters					Endpoints Assessed	Results (Effects/NOEL/LOEL)		Comments
	Chemical (Source/ Purity/ Preparation)	Animal Model (Species/ Strain/Sex/ Age) N	Study Design	Exposure (Route/Period/ Frequency/ Vehicle)	Doses/ Concen-trations		Systemic Toxicity	Reproductive Toxicity	
Wood 1981	Chlorsulfuron Purity 92-95%	CD® rats, males and females Mated at 90-103 days of age 20/sex/group	3 generation reproduction study (Male and female rats from a two-year feeding study received the chemical in the diet for 103 days and then were allowed to mate for a 15 day period) 6 litters (2 litters per generation) F1a, F1 b F2a, F2b F3a, F3b F1b → F2 generation; F2b -→ F3 generation	Oral (diet)	0, 100, 500, 2500 ppm	Food consumption, body weights and weight gains, organ weights and clinical measurements (erythrocyte counts and other hematological effects) from feeding study. For the Reproduction study - Clinical observations, mean number of pups/litter, gestation, lactation and viability indices, litter survival, mean weanling body weights and weight gains Histopathology of organs from 21 day old F3b animals	Decreased body weights and body weight gains in males at 2500 ppm. Short-lived dose-dependent decreases in erythrocyte counts and other hematological effects during the first year of the study observed at 500 and 2500 ppm. Reported Systemic NOEL = 100	Decrease in fertility index at 2500 ppm for F2b animals. 95% in controls vs. 79% for both F2b matings (to produce F3a and F3b groups) Reported Reproductive NOEL = 500 ppm	Subpart of combined study (Two-year feeding study and 3 generation reproduction study).
Munley 2011 Supplement 3, Revision 1 to Wood 1981	Supplemental analysis of data from Wood (1981). The following additional material and analyses were provided: 1. Relevant Historical Control Data (1974-1983) to aid in the interpretation of fertility index data from the original study. 2. Conclusions from the additional review and the results of the additional statistical analyses of fertility index data for F3a and F3b (Cochran Armitage Test). 3. Male Fertility index data showing individual matings for F2b animals to result in F3a and F3b to aid in the interpretation of the findings for the third generation. 4. Correction of minor report errors The historical control data for fertility index collected between 1974 and 1983 provided in the supplement ranged from 60-100%. Only 6 of the 12 studies had a third generation and the authors compared the fertility index of the chlorsulfuron study to F1 to F3 values and concluded that all data from the current study fell well within the ranges seen in historical control groups. Results of individual mating data for each pairing of males and females provided in the supplement demonstrate that females unsuccessful in first pairing were successful in subsequent pairings. Authors stated there was no significant lack of mating success in any treatment group by step-down exact permutation Cochran-Armitage test. For males, 3 individuals #257753, #257755, #257757 were found to be unsuccessful in both pairings								

Munley 2012b Supplement 3, Revision 2 to Wood 1981	Supplemental analysis of data from Wood (1981). Prepared to clarify information in the previous Revision 1 and to put the study in perspective in view of the more recent multigeneration reproduction study. Details to the statistical analysis section specifying the mating pairs were included in the analysis The authors reiterated the information about the historical data. In the section which provides the Cochran-Armitage trend test calculations, the values for both the asymptotic and exact tests were previously provided as the direct output from the statistical analysis software. In this review, the authors state that for the current data sets, the exact test calculations were the most appropriate given the sample sizes and accordingly, the exact test results were provided and the asymptotic values were removed. Also chi-square analysis was used to analyze fertility data. In the conclusions the authors state that the female fertility indices of all the control and treatment groups on study ranged from 79 to 100%, and were well within the historical control range of 60 to 100%. In addition, they stated that there were "problems in longevity and reproductive performance" in Sprague-Dawley rats as a result of inbreeding practices that were in place around the time of the conduct of the study. The authors concluded that no effects on fertility were evident in the subsequent multigeneration reproductive toxicity study which tested dietary concentrations of up to 7500 ppm, a dose that is three times higher than the highest dose of the 1981 study. They reported that statistical analyses of the Generation 3A and 3B litter data showed no significant treatment effect in any dose group and both the Cochran-Armitage test and a chi-square analysis showed that there were no significant decreases in mating success in any treatment group, both by trend and pair-wise assessments, respectively. The authors mention that for males, 3 individuals #257753, #257755, #257757 were found to be unsuccessful in both pairing and also state that the study was conducted prior to the male proven breeder program (in which all males destined to become breeders would undergo an initial timed mating with a known fertile female and sire a litter before being admitted into the breeding program) possibly explaining the less than optimal fertility in the rats.

Appendix A: Parameters for Literature Searches on the Reproductive Toxicity of Chemicals

Searches of the literature on the reproductive and developmental toxicity of the chemicals in Tables 1 and 2 were conducted under contract by the University of California at Berkeley (Charleen Kubota, M.L.I.S.). The goal was to identify peer-reviewed open source and proprietary journal articles, print and digital books, reports and gray literature that potentially reported relevant toxicological and epidemiological information on the reproductive toxicity of the chemicals. The search sought to specifically identify all literature relevant to the assessment of evidence on male reproductive, female reproductive and developmental toxicity.

Databases

The literature search utilized the following search platforms/database vendors:
ChemSpider (Royal Society of Chemistry)
MeSH (Medical Subject Headings) (National Library of Medicine)
Developmental and Reproductive Toxicology Database (DART/ETIC) (National Library of Medicine)
EMBASE® (Elsevier)
Environmental Sciences and Pollution Management (Proquest)
PubMed (National Library of Medicine)
National Technical Research Library (NTRL v3.0) (National Technical Information Service)
ReproRisk® System: **REPROTEXT®** Reproductive Hazard Reference**, REPROTOX®** Reproductive Hazard Information, **Shepard's Catalog of Teratogenic Agents**, **TERIS Teratogen Information System (RightAnswer® Knowledge Solutions OnSite™ Applications)**
Scifinder®: CAS (Chemical Abstracts Service)
TOXLINE (National Library of Medicine)
Web of Knowledge: BIOSIS Previews®, Web of Science® (Thomson-Reuters, Inc.)

Search Process

ChemSpider was searched first to gather chemical names, synonyms, CAS registry numbers, MeSH and Chemical Abstracts Service headings for each substance before searching bibliographic databases. The MeSH database was used to identify relevant subject headings for reproductive and developmental toxicology endpoints. Relevant subject terms were entered into the PubMed Search Builder to execute a PubMed search.

The following is a typical DART chemical search strategy used to search PubMed:

("*chemical name*" [MeSh] OR CAS *registry number*[RN]) AND ("Congenital Abnormalities"[MeSh] OR "Pregnancy Complications"[MeSh] OR "Reproductive Physiological Phenomena"[MeSh] OR "Embryonic and Fetal Development"[MeSH])
In PubMed, MeSH (Medical Subject Headings) terms at the top of hierarchical lists of subject headings are automatically "exploded" in a search to retrieve citations with more specific MeSH terms. For example, the heading "Congenital Abnormalities" includes numerous specific conditions such as spina bifida and congenital heart defects. The broad subject heading "Pregnancy Complications" encompasses multiple conditions or pathological processes associated with pregnancy. Spontaneous abortion and many fetal diseases are listed under this term.

Additional databases listed above were then searched for each chemical. The search strategies were tailored according to the search features unique to each database. Web of Science, for example, was searched by entering chemical terms and refining the search by applying Web of Science categories Developmental Biology, Toxicology and/or Public, Environmental and Occupational Health. Sometimes other databases not listed here were searched as needed. For example, if there is a known behavioral endpoint linked to chemical exposure, a social science database such as PsycINFO® would be searched.