

## APPENDIX B. LITERATURE SEARCH FRAMEWORK FOR DINITROCRESOLS

The objective of the toxicological profile is to evaluate the potential for human exposure and the potential health hazards associated with inhalation, oral, or dermal/ocular exposure to dinitrocresols.

### B.1 LITERATURE SEARCH AND SCREEN

A literature search and screen was conducted to identify studies examining health effects, toxicokinetics, mechanisms of action, susceptible populations, biomarkers, and chemical interactions data for dinitrocresols. ATSDR primarily focused on peer-reviewed articles without publication date or language restrictions. Non-peer-reviewed studies that were considered relevant to the assessment of the health effects of dinitrocresols have undergone peer review by at least three ATSDR-selected experts who have been screened for conflict of interest. The inclusion criteria used to identify relevant studies examining the health effects of dinitrocresols are presented in Table B-1.

**Table B-1. Inclusion Criteria for the Literature Search and Screen**

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Health Effects

Species

Human

Laboratory mammals

Route of exposure

Inhalation

Oral

Dermal (or ocular)

Parenteral (these studies will be considered supporting data)

Health outcome

Death

Systemic effects

Body weight effects

Respiratory effects

Cardiovascular effects

Gastrointestinal effects

Hematological effects

Musculoskeletal effects

Hepatic effects

Renal effects

Dermal effects

Ocular effects

Endocrine effects

Immunological effects

Neurological effects

Reproductive effects

Developmental effects

Other noncancer effects

**Table B-1. Inclusion Criteria for the Literature Search and Screen**

Cancer
Toxicokinetics
Absorption
Distribution
Metabolism
Excretion
PBPK models
Biomarkers
Biomarkers of exposure
Biomarkers of effect
Interactions with other chemicals

### B.1.1 Literature Search

The current literature search was intended to update the health effects sections of the existing toxicological profile for dinitrocresols (ATSDR 1995), thus, the literature search was restricted to studies published between January 1993 to March 2017. The following main databases were searched in March 2017:

- PubMed
- National Library of Medicine's TOXLINE
- Scientific and Technical Information Network's TOXCENTER

The search strategy used the chemical names, Chemical Abstracts Service (CAS) numbers, synonyms, Medical Subject Headings (MeSH) headings, and keywords for dinitrocresols. The query strings used for the literature search are presented in Table B-2.

The search was augmented by searching the Toxic Substances Control Act Test Submissions (TSCATS), NTP website, and National Institute of Health Research Portfolio Online Reporting Tools Expenditures and Results (NIH RePORTER) databases using the queries presented in Table B-3. Additional databases were searched in the creation of various tables and figures, such as the TRI Explorer, the Substance Priority List (SPL) resource page, and other items as needed. Regulations applicable to dinitrocresols were identified by searching international and U.S. agency websites and documents.

Review articles were identified and used for the purpose of providing background information and identifying additional references. ATSDR also identified reports from the grey literature, which included unpublished research reports, technical reports from government agencies, conference proceedings and abstracts, and theses and dissertations.

**Table B-2. Database Query Strings**

Database	search date	Query string
<b>PubMed</b>		
	03/2017	((("2,4-Dinitro-5-methylphenol"[tw] OR "3-Methyl-4,6-dinitrophenol"[tw] OR "4,6-Dinitro-m-cresol"[tw] OR "5-methyl-2,4-dinitro-Phenol"[tw]) AND (1993/01/01 : 3000[dp] OR

Table B-2. Database Query Strings

Database search date	Query string
	<p>1993/01/01 : 3000[crdat] OR 1993/01/01 : 3000[edat])) OR ((534-52-1[rn] OR 1604ZJR09T[rn] OR "4,6-dinitro-o-cresol"[supplementary concept] OR "4,6-dinitro-o-cresol"[nm]) AND (1993/01/01 : 3000[dp] OR 1993/01/01 : 3000[mhda])) OR (("3,5-Dinitro-o-cresol"[tw] OR "2-methyl-3,5-dinitro-Phenol"[tw] OR "3,5-Dinitro-ortho-cresol"[tw]) AND (1993/01/01 : 3000[dp] OR 1993/01/01 : 3000[crdat] OR 1993/01/01 : 3000[edat])) OR ((609-93-8[rn] OR L572BVH6NF[rn] OR "2,6-dinitro-p-cresol"[supplementary concept] OR "2,6-dinitro-p-cresol"[nm]) AND (1993/01/01 : 3000[dp] OR 1993/01/01 : 3000[mhda])) OR (((("2,4-Dinitro-6-methylphenol"[tw] OR "2,4-Dinitro-o-cresol"[tw] OR "2-Methyl-4,6-dinitrophenol"[tw] OR "3,5-Dinitro-2-hydroxytoluene"[tw] OR "4,6-dinitro-2-cresol"[tw] OR "4,6-Dinitro-o-cresol"[tw] OR "4,6-dinitro-ortho-cresol"[tw] OR "4,6-Dinitro-o-cresolo"[tw] OR "4,6-Dinitro-o-kresol"[tw] OR "4,6-Dinitrokresol"[tw] OR "6-Methyl-2,4-dinitrophenol"[tw] OR "Antinonin"[tw] OR "Antinonnin"[tw] OR "Arborol"[tw] OR "Capsine"[tw] OR "Chemsect DNOC"[tw] OR "Degrassan"[tw] OR "Dekrysil"[tw] OR "Detal"[tw] OR "Dillex"[tw] OR "Dinitro"[tw] OR "Dinitro-o-cresol"[tw] OR "Dinitrocresol"[tw] OR "Dinitrodendtroxal"[tw] OR "Dinitrol"[tw] OR "Dinoc"[tw] OR "Dinurania"[tw] OR "Ditrosol"[tw] OR "Dn-dry mix no. 2"[tw] OR "DNOC"[tw] OR "DNOK"[tw] OR "Dwunitro-o-krezol"[tw] OR "Effusan"[tw] OR "Effusan 3436"[tw] OR "Elgetol"[tw] OR "Elgetol 30"[tw] OR "Elipol"[tw] OR "Extrar"[tw] OR "Flavin-Samdoz"[tw] OR "Hedolit"[tw] OR "Hedolite"[tw] OR "Kreozan"[tw] OR "Kresamone"[tw] OR "Kresonite-E"[tw] OR "Krezotol 50"[tw] OR "LE dinitrocresol-4,6"[tw] OR "Lipan"[tw] OR "Neudorff DN 50"[tw] OR "Nitrador"[tw] OR "Nitrofan"[tw] OR "Oranz viktoria"[tw] OR "Prokarbol"[tw] OR "Rafex"[tw] OR "Rafex 35"[tw] OR "Raphatox"[tw] OR "Sandolin"[tw] OR "Sandolin A"[tw] OR "Selinon"[tw] OR "Sinox"[tw] OR "3,5-dinitro-2-hydroxy-Toluene"[tw] OR "Trifocide"[tw] OR "Trifrina"[tw] OR "Winterwash"[tw] OR "Zahlreiche bezeichnungen"[tw]) NOT medline[sb]) AND (1993/01/01 : 3000[dp] OR 1993/01/01 : 3000[crdat] OR 1993/01/01 : 3000[edat])) OR ((("2,6-Dinitro-4-methylphenol"[tw] OR "2,6-Dinitro-p-cresol"[tw] OR "4-Methyl-2,6-dinitrophenol"[tw] OR "Dinitro-p-cresol"[tw] OR "DNPC"[tw] OR "3,5-dinitro-4-hydroxy-Toluene"[tw] OR "Victoria Orange"[tw] OR "Victoria Yellow"[tw] OR "Dinitro-para-cresol"[tw]) AND (1993/01/01 : 3000[dp] OR 1993/01/01 : 3000[crdat] OR 1993/01/01 : 3000[edat]))) OR ((Dinitrocresols[MeSH] AND (1993/01/01 : 3000[dp] OR 1993/01/01 : 3000[mhda])) OR (("Dinitrocresols"[tw] NOT medline[sb]) AND (1993/01/01 : 3000[dp] OR 1993/01/01 : 3000[crdat] OR 1993/01/01 : 3000[edat])))</p>
<b>Toxline</b>	
03/2017	<p>( 616-73-9 [rn] OR 534-52-1 [rn] OR 497-56-3 [rn] OR 609-93-8 [rn] OR "2 4 dinitro 5 methylphenol" OR "3 methyl 4 6 dinitrophenol" OR "4 6 dinitro m cresol" OR "5 methyl 2 4 dinitro phenol" OR "2 4 dinitro 6 methylphenol" OR "2 4 dinitro o cresol" OR "2 methyl 4 6 dinitrophenol" OR "3 5 dinitro 2 hydroxytoluene" OR "4 6 dinitro 2 cresol" OR "4 6 dinitro o cresol" OR "4 6 dinitro ortho cresol" OR "4 6 dinitro o cresolo" OR "4 6 dinitro o kresol" OR "4 6 dinitrokresol" OR "6 methyl 2 4 dinitrophenol" OR "antinonin" OR "antinonnin" OR "arborol" OR "capsine" OR "chemsect dnoc" OR "degrassan" OR "dekrysil" OR "detal" OR "dillex" OR "dinitro" OR "dinitro o cresol" OR "dinitrocresol" OR "dinitrodendtroxal" OR "dinitrol" OR "dinoc" OR "dinurania" OR "ditrosol" OR "dn dry mix no 2" OR "dnoc" OR "dnok" OR "dwunitro o krezol" OR "effusan" OR "effusan 3436" OR "elgetol" OR "elgetol 30" OR "elipol" OR "extrar" OR "flavin samdoz" OR "hedolit" OR "hedolite" OR "kreozan" OR "kresamone" OR "kresonite e" OR "krezotol 50" OR "le dinitrocresol 4 6" OR "lipan" OR "neudorff dn 50" OR "nitrador" OR "nitrofan" OR "oranz viktoria" OR "prokarbol" OR "rafex" OR "rafex 35" OR "raphatox" OR "sandolin" OR "sandolin a" OR "selinon" OR "sinox" OR "3 5 dinitro 2 hydroxy toluene" OR "trifocide" OR "trifrina" OR "winterwash" OR "zahlreiche bezeichnungen" OR "3 5 dinitro o cresol" OR "2 methyl 3 5 dinitro phenol" OR "3 5 dinitro ortho cresol" OR "2 6 dinitro 4 methylphenol" OR "2 6 dinitro p cresol" OR "4 methyl 2 6 dinitrophenol" OR "dinitro p cresol" OR "dnpc" OR "3 5 dinitro 4 hydroxy</p>

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**Table B-2. Database Query Strings**

Database	search date	Query string
		toluene" OR "victoria orange" OR "victoria yellow" OR "dinitro para cresol") AND 1993:2017 [yr] AND ( ANEUPL [org] OR BIOSIS [org] OR CIS [org] OR DART [org] OR EMIC [org] OR EPIDEM [org] OR HEEP [org] OR HMTC [org] OR IPA [org] OR RISKLINE [org] OR MTGABS [org] OR NIOSH [org] OR NTIS [org] OR PESTAB [org] OR PPBIB [org] ) AND NOT PubMed [org] AND NOT pubdart [org]
<b>Toxcenter</b>		
03/2017		FILE 'TOXCENTER' ENTERED AT 09:29:55 ON 29 MAR 2017
	L1	1948 SEA 616-73-9 OR 534-52-1 OR 497-56-3 OR 609-93-8
	L2	14 SEA 12167-18-9
	L3	1960 SEA L1 OR L2
	L4	1937 SEA L3 NOT TSCATS/FS
	L5	1752 SEA L4 NOT PATENT/DT
	L6	694 SEA L5 AND PY>=1993 ACTIVATE TOXQUERY/Q -----
	L7	QUE (CHRONIC OR IMMUNOTOX? OR NEUROTOX? OR TOXICOKIN? OR BIOMARKER? OR NEUROLOG?)
	L8	QUE (PHARMACOKIN? OR SUBCHRONIC OR PBPK OR EPIDEMIOLOGY/ST,CT, IT)
	L9	QUE (ACUTE OR SUBACUTE OR LD50# OR LD(W)50 OR LC50# OR LC(W)50)
	L10	QUE (TOXICITY OR ADVERSE OR POISONING)/ST,CT,IT
	L11	QUE (INHAL? OR PULMON? OR NASAL? OR LUNG? OR RESPIR?)
	L12	QUE ((OCCUPATION? OR WORKPLACE? OR WORKER?) AND EXPOS?)
	L13	QUE (ORAL OR ORALLY OR INGEST? OR GAVAGE? OR DIET OR DIETS OR DIETARY OR DRINKING(W)WATER?)
	L14	QUE (MAXIMUM AND CONCENTRATION? AND (ALLOWABLE OR PERMISSIBLE))
	L15	QUE (ABORT? OR ABNORMALIT? OR EMBRYO? OR CLEFT? OR FETUS?)
	L16	QUE (FOETUS? OR FETAL? OR FOETAL? OR FERTIL? OR MALFORM? OR OVUM?)
	L17	QUE (OVA OR OVARY OR PLACENTA? OR PREGNAN? OR PRENATAL?)
	L18	QUE (PERINATAL? OR POSTNATAL? OR REPRODUC? OR STERIL? OR TERATOGEN?)
	L19	QUE (SPERM OR SPERMAC? OR SPERMAG? OR SPERMATI? OR SPERMAS? OR SPERMATOB? OR SPERMATOC? OR SPERMATOG?)
	L20	QUE (SPERMATOI? OR SPERMATOL? OR SPERMATOR? OR SPERMATOX? OR SPERMATOZ? OR SPERMATU? OR SPERMI? OR SPERMO?)
	L21	QUE (NEONAT? OR NEWBORN? OR DEVELOPMENT OR DEVELOPMENTAL?)
	L22	QUE (ENDOCRIN? AND DISRUPT?)
	L23	QUE (ZYGOTE? OR CHILD OR CHILDREN OR ADOLESCEN? OR INFANT?)
	L24	QUE (WEAN? OR OFFSPRING OR AGE(W)FACTOR?)

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**Table B-2. Database Query Strings**

Database search date	Query string
L25	QUE (DERMAL? OR DERMIS OR SKIN OR EPIDERM? OR CUTANEOUS?)
L26	QUE (CARCINO? OR COCARCINO? OR CANCER? OR PRECANCER?
OR	
	NEOPLAS?)
L27	QUE (TUMOR? OR TUMOUR? OR ONCOGEN? OR LYMPHOMA? OR
	CARCINOM?)
L28	QUE (GENETOX? OR GENOTOX? OR MUTAGEN? OR
	GENETIC(W)TOXIC?)
L29	QUE (NEPHROTOX? OR HEPATOTOX?)
L30	QUE (ENDOCRIN? OR ESTROGEN? OR ANDROGEN? OR HORMON?)
L31	QUE (OCCUPATION? OR WORKER? OR WORKPLACE? OR EPIDEM?)
L32	QUE L7 OR L8 OR L9 OR L10 OR L11 OR L12 OR L13 OR L14 OR L15
	OR L16 OR L17 OR L18 OR L19 OR L20 OR L21 OR L22 OR L23 OR L24
	OR L25 OR L26 OR L27 OR L28 OR L29 OR L30 OR L31
L33	QUE (RAT OR RATS OR MOUSE OR MICE OR GUINEA(W)PIG? OR
MURIDAE	
	OR DOG OR DOGS OR RABBIT? OR HAMSTER? OR PIG OR PIGS OR
SWINE	
	OR PORCINE OR MONKEY? OR MACAQUE?)
L34	QUE (MARMOSET? OR FERRET? OR GERBIL? OR RODENT? OR
LAGOMORPHA	
	OR BABOON? OR CANINE OR CAT OR CATS OR FELINE OR MURINE)
L35	QUE L32 OR L33 OR L34
L36	QUE (NONHUMAN MAMMALS)/ORGN
L37	QUE L35 OR L36
L38	QUE (HUMAN OR HUMANS OR HOMINIDAE OR MAMMALS OR MAMMAL?
OR	
	PRIMATES OR PRIMATE?)
L39	QUE L37 OR L38
	-----
L40	344 SEA L6 AND L39
L41	24 SEA L40 AND MEDLINE/FS
L42	17 SEA L40 AND BIOSIS/FS
L43	297 SEA L40 AND CAPLUS/FS
L44	6 SEA L40 NOT (MEDLINE/FS OR BIOSIS/FS OR CAPLUS/FS)
L45	321 DUP REM L41 L42 L44 L43 (23 DUPLICATES REMOVED)
L*** DEL	24 S L40 AND MEDLINE/FS
L*** DEL	24 S L40 AND MEDLINE/FS
L46	24 SEA L45
L*** DEL	17 S L40 AND BIOSIS/FS
L*** DEL	17 S L40 AND BIOSIS/FS
L47	14 SEA L45
L*** DEL	297 S L40 AND CAPLUS/FS
L*** DEL	297 S L40 AND CAPLUS/FS
L48	278 SEA L45
L*** DEL	6 S L40 NOT (MEDLINE/FS OR BIOSIS/FS OR CAPLUS/FS)
L*** DEL	6 S L40 NOT (MEDLINE/FS OR BIOSIS/FS OR CAPLUS/FS)
L49	5 SEA L45
L50	297 SEA (L46 OR L47 OR L48 OR L49) NOT MEDLINE/FS
L51	278 SEA L50 AND CAPLUS/FS

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**Table B-2. Database Query Strings**

Database	search date	Query string
		D SCAN L50

**Table B-3. Strategies to Augment the Literature Search**

Source	Query and number screened when available
<b>TSCATS<sup>a</sup></b>	
03/2017	Compounds searched: 616-73-9, 534-52-1, 497-56-3, 609-93-8, 12167-18-9
<b>NTP</b>	
03/2017	616-73-9 534-52-1 497-56-3 609-93-8 12167-18-9 2,4-Dinitro-5-methylphenol 3-Methyl-4,6-dinitrophenol 4,6-Dinitro-m-cresol 5-methyl-2,4-dinitro-Phenol 2,4-Dinitro-6-methylphenol 2,4-Dinitro-o-cresol 2-Methyl-4,6-dinitrophenol 3,5-Dinitro-2-hydroxytoluene 4,6-dinitro-2-cresol 4,6-Dinitro-o-cresol 4,6-dinitro-ortho-cresol 6-Methyl-2,4-dinitrophenol DNOC 3,5-Dinitro-o-cresol 2-methyl-3,5-dinitro-Phenol 3,5-Dinitro-ortho-cresol 2,6-Dinitro-4-methylphenol 2,6-Dinitro-p-cresol 4-Methyl-2,6-dinitrophenol Dinitro-p-cresol Dinitro-para-cresol DNPC 3,5-dinitro-4-hydroxy-Toluene Dinitrocresols Dinitrocresol
<b>NIH RePORTER</b>	
06/2017	Text Search: "2,4-Dinitro-6-methylphenol" OR "2,4-Dinitro-o-cresol" OR "2-Methyl-4,6-dinitrophenol " OR "3,5-Dinitro-2-hydroxytoluene" OR "4,6-dinitro-2-cresol" OR "4,6-Dinitro-o-cresol" OR "4,6-dinitro-ortho-cresol" OR "4,6-Dinitro-o-cresolo" OR "4,6-Dinitro-o-kresol" OR "4,6-Dinitrokresol" OR "6-Methyl-2,4-dinitrophenol" OR "Antinonin" OR "Antinonnin" OR "Arborol" OR "Capsine" OR "Chemsect DNOC" OR "Degrassan" OR "Dekrysil" OR "Detal" OR "Dillex" OR "Dinitro" OR "Dinitro-o-cresol" OR "Dinitrocresol" OR "Dinitrodendtroxal" OR "Dinitrol" OR "Dinoc" OR "Dinurania" OR "Ditrosol" OR "Dn-dry mix no. 2" OR "DNOC" OR "DNOK" OR "Dwunitro-o-krezol" OR

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**Table B-3. Strategies to Augment the Literature Search**

Source	Query and number screened when available
	"Effusan" OR "Effusan 3436" OR "Elgetol" OR "Elgetol 30" OR "Elipol" OR "Extrar" OR "Flavin-Samdoz" OR "Hedolit" OR "Hedolite" OR "Kreozan" OR "Kresamone" OR "Kresonite-E" OR "Krezotol 50" OR "LE dinitrocresol-4,6" OR "Lipan" OR "Neudorff DN 50" OR "Nitrador" OR "Nitrofan" OR "Oranz viktoria" OR "Prokarbol" OR "Rafex" OR "Rafex 35" OR "Raphatox" OR "Sandolin" OR "Sandolin A" OR "Selinon" OR "Sinox" OR "Trifocide" OR "Trifrina" OR "Winterwash" OR "Zahlreiche bezeichnungen" (Advanced), Search in: Projects AdminIC: All, Fiscal Year: Active Projects
<b>Other</b>	Identified throughout the assessment process

<sup>a</sup>Several versions of the TSCATS database were searched, as needed, by CASRN including TSCATS1 via Toxline (no date limit), TSCATS2 via <https://yosemite.epa.gov/oppts/epatscat8.nsf/ReportSearch?OpenForm> (date restricted by EPA receipt date), and TSCATS via CDAT (date restricted by 'Mail Received Date Range'), as well as google for recent TSCA submissions.

The 2017 results were:

- Number of records identified from PubMed, TOXLINE, and TOXCENTER (after duplicate removal): 1,003
- Number of records identified from other strategies: 35
- Total number of records to undergo literature screening: 1,038

### B.1.2 Literature Screening

A two-step process was used to screen the literature search to identify relevant studies on dinitrocresols:

- Title and abstract screen
- Full text screen

**Title and Abstract Screen.** Within the reference library, titles and abstracts were screened manually for relevance. Studies that were considered relevant (see Table B-1 for inclusion criteria) were moved to the second step of the literature screening process. Studies were excluded when the title and abstract clearly indicated that the study was not relevant to the toxicological profile.

- Number of titles and abstracts screened: 1,038
- Number of studies considered relevant and moved to the next step: 47

**Full Text Screen.** The second step in the literature screening process was a full text review of individual studies considered relevant in the title and abstract screen step. Each study was reviewed to determine whether it was relevant for inclusion in the toxicological profile.

- Number of studies undergoing full text review: 47
- Number of studies cited in the health effects sections of the existing toxicological profile (August, 1995): 78
- Total number of studies cited in the health effects sections of the updated profile: 90

A summary of the results of the literature search and screening is presented in Figure B-1.

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**Figure B-1. March 2017 Literature Search Results and Screen for Dinitrocresols**