Draft RoC Monograph for *ortho*-Toluidine: Literature Search Strategy and Preliminary List of References

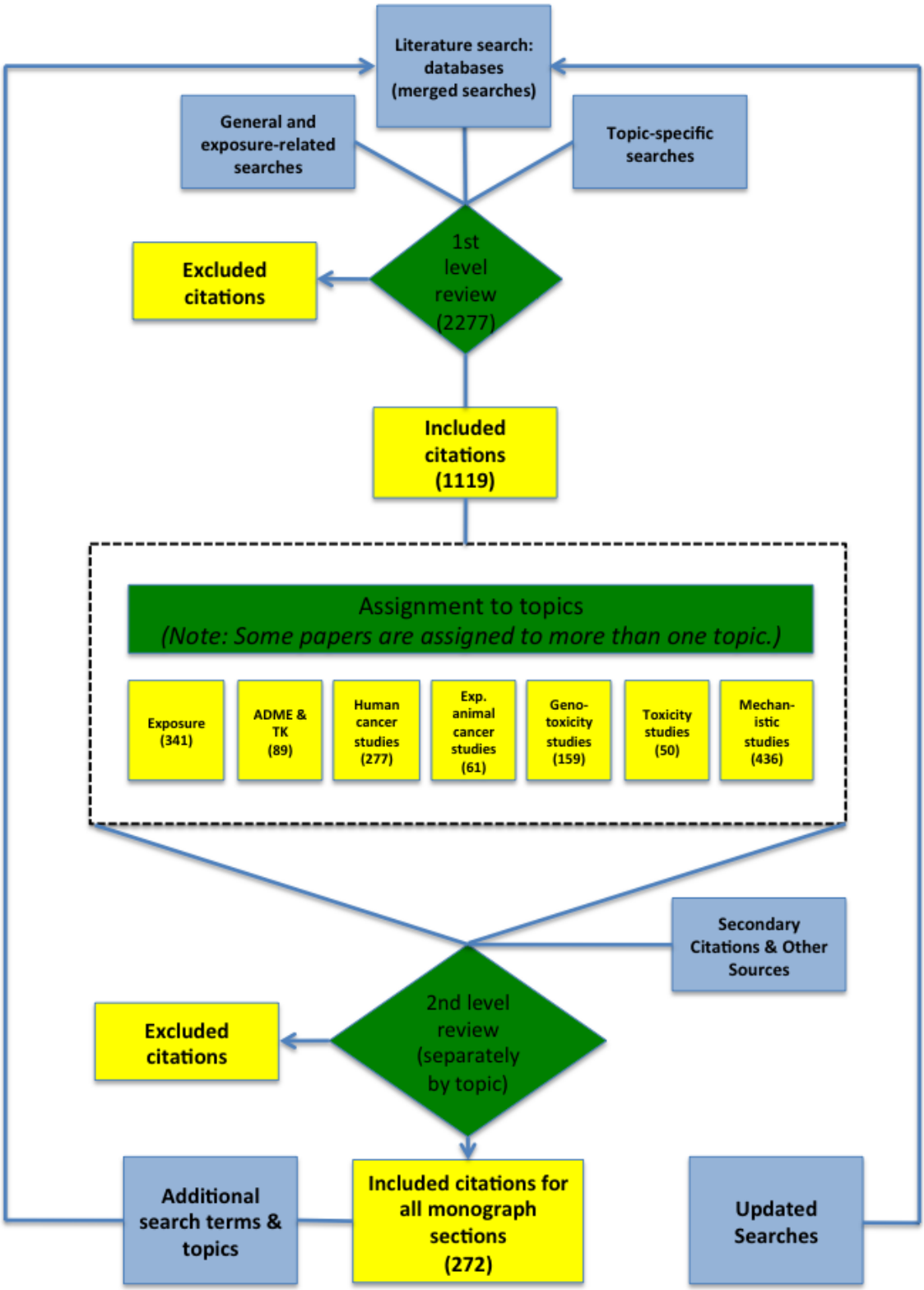
This document describes the data sources, search terms, and search strategies that were used to identify literature for the draft monograph on *ortho*-toluidine (CASRN 95-53-4). The literature search strategy used for *ortho*-toluidine involved several approaches designed to identify potentially useful information for the broad range of topics covered by a Report on Carcinogens (RoC) monograph, as listed below.

- Properties and Human Exposure (focusing on the U.S. population)
- Disposition (ADME) and Toxicokinetics
- Human Cancer Studies
- Studies of Cancer in Experimental Animals
- Mechanistic Data and Other Relevant Effects
  - Genetic and Related Effects
  - Mechanistic Considerations

The methods for identifying the relevant literature for the draft *ortho*-toluidine monograph, including (Part I) the search strategy, (Part II) updating the literature search, and (Part III) the review of citations using web-based systematic review software, are illustrated in Figure 1 and discussed below. Part IV provides information on general searches for potential confounders identified from epidemiologic studies of *ortho*-toluidine.

The preliminary list of references used in the preparation of the draft RoC monograph on *ortho*-toluidine is provided in Part V at the end of this document.

Figure 1. Literature search strategy and review



Part I. Search strategy

Because *ortho*-toluidine has been listed in the Report on Carcinogens as *reasonably anticipated to be a human carcinogen* since 1983, the literature search strategy is based on updating information published since the time period covered by the previous review (i.e., since 1982).

As mentioned in the concept document for *ortho*-toluidine, the monograph focuses on human cancer studies and mechanistic data, and thus extensive literature searches were conducted to identify this information. Searches were also conducted for studies of cancer in experimental animals published since the first listing of *ortho*-toluidine in the RoC (1982). The monograph relies primarily on authoritative reviews for information on exposure, toxicokinetics, and genotoxicity, but literature searches were conducted to update that information from the date of the most recent comprehensive review by IARC (Working group met in 2008, literature searches were conducted from 2007). Searches were conducted to identify other major authoritative reviews (see Table 1).

Table 1: Preliminary literature search approach (from RoC concept document)

Topic	Combined with	Date/limits
Human exposure	*ortho*-toluidine synonyms	Reviews Primary literature: since 2007
Studies in experimental animals	*ortho*-toluidine synonyms *ortho*-toluidine hydrochloride and CASRN	Primary literature since 1982
ADME and Toxicokinetics	*ortho*-toluidine synonyms *ortho*-toluidine metabolites[a]	Reviews Primary literature: since 2007
Genotoxicity	*ortho*-toluidine synonyms *ortho*-toluidine metabolites[a]	Reviews Primary literature: since 2007
Toxicity	*ortho*-toluidine synonyms *ortho*-toluidine metabolites[a]	Reviews Primary literature: since 2007
Mechanisms	ortho-toluidine synonyms ortho-toluidine metabolites[a] aromatic amines	No limits Includes searches for animal cancer studies of metabolites

ADME = adsorption, distribution, metabolism and excretion

[a] Major metabolites include azoxytoluene, *o*-nitrosotoluene, *N*-acetyl-*o*-toluidine, *N*-acetyl-*o*-aminobenzyl alcohol, 4-amino-*m*-cresol, *N*-acetyl-4-amino-*m*-cresol, anthranilic acid, and *N*-acetylanthranilic acid.

Relevant literature is identified using search terms, data sources, and strategies as described below.

1. **General data search:** This search covers a broad range of general data sources (see Table 2a,b,c) for information relevant to many or all of the wide range of monograph topics pertaining to *ortho*-toluidine.
2. **Exposure-related data search:** This search covers a broad range of potential sources (see Table 3) for exposure-related information and physical-chemical properties.

3. **Database searches in PubMed, Scopus, and Web of Science:** The majority of the primary literature used to draft the *ortho*-toluidine monograph was identified from searches of these three extensive databases available through the NIEHS Library. Synonyms, metabolites, and the chemical class for *ortho*-toluidine were identified from the sources listed in Table 4 and the search terms are listed in Table 5. Information on metabolites and structurally related chemicals may be important for evaluating potential mechanisms of carcinogenicity. These searches were combined with the search terms listed in Table 5 for each of the monograph topics listed above to create the specific literature searches in Table 6. See Table 5 for details on this approach and Table 6 for topic-specific search terms.

   Searches for human cancer studies are somewhat unique because they involve the identification of search terms for exposure scenarios that might result in exposure of people to *ortho*-toluidine. For *ortho*-toluidine, these exposure-related search terms were based on its use in the manufacture of dyes, rubber chemicals, and a herbicide intermediate, and those search terms were combined with search terms specific for human cancer.

4. **QUOSA library of occupational case-control studies** search of the QUOSA-based library of approximately 6,000 occupational case-control studies, approximately 60% of which are currently available as searchable full-text pdfs, was conducted using the synonyms “o-toluidine”, “ortho-toluidine”, “95-53-4”, “2-toluidine”, “1-amino-2-methylbenzene”, “2-amino-1-methylbenzene”, “2-aminotoluene”, “o-aminotoluene”, “ortho-aminotoluene”, “2-methyl-1-aminobenzene”, “2-methylaniline”, “o-methylaniline”, “ortho-methylaniline”, “o-methylbenzenamine”, “ortho-methylbenzenamine”, “2-methylphenylamine”, “2-tolylamine”, “o-tolylamine”, “ortho-tolylamine.”

5. **Special topic-focused searches:** No special topic-focused searches were conducted for *ortho*-toluidine, but searches for general information on potential confounders were conducted.

6. **Secondary sources:** Citations identified from authoritative reviews or from primary references located by literature search, together with publications citing key papers identified using the Web of Science “Cited Reference Search,” were also added.

General Sources Checklist for: *o*-Toluidine

Table 2a. Comprehensive sources or reviews

Source	Name of document
1) NTP technical reports	NTP1996
2) NTP nomination for toxicological evaluation documents	--
3) OHAT (formerly CERHR)	--
4) Public comments to the technical report subcommittee	--
5) IARC monographs	IARC2012 IARC2010 IARC2000 IARC1987 IARC1982 IARC1978
6) ATSDR Toxicological Profiles	--
7) EPA IRIS	--
8) NAS Reports and Publications	--
9) WHO (IPCS) INCHEM-related documents (a-k below)	
a) CICADS	WHO1998
b) EHC	--
c) HSGs	--
d) ICSCs	IPCS2009
e) JECFA	--
f) JMPR	--
g) KemI-Riskline	--
h) PDs	--
i) PIMS	--
j) SIDS	OECD2004
k) UKPID	--
10) California EPA Prop 65 hazard identification documents	--
11) Health Canada	HC2009
12) New York State Department of Health- Health Topics A to Z	--

Table 2b. General information sources

Source	Name of document
1) U.S. National Library of Medicine (NLM)- TOXNET	
a) HSDB	HSDB2005
b) CCRIS	CCRIS2011a CCRIS2011b
c) GENETOX	GENETOX1991a GENETOX1991b
d) ITER	--
e) LactMed	--
f) CPD	CPDB2007
g) CTD	CTD2012
2) PubChem	PubChem2012a PubChem2012b
3) Kirk-Othmer Encyclopedia- (Downloaded Gregory2009- Article on "Dyes and Dye Intermediates," but no mention of *ortho*-toluidine)	Gregory2009
4) USGS (Minerals	--

Table 2c. European Union – sources to search

Source	Name of document
1) International Uniform Chemical Information Database (IUCLID)	IUCLID2000
2) European Chemicals Agency	
3) The International Portal on Food Safety, Animal and Plant Health (IPFSAPH)	--
4) The European Food Safety Authority	--
5) European Centre for Disease Prevention and Control (ECDC)	--
6) European Monitoring Centre for Drugs and Drug Addiction	--
7) International Labour Organization (ILO)	--
8) United Nations Environment Programme (UNEP)	--

Exposure-related sources checklist for: *ortho*-Toluidine

Table 3. Exposure- and properties-specific sources

Source	Name of document
1) U.S. National Library of Medicine (NLM)- TOXNET	
a) ChemIDplus	ChemID2012
b) Haz-Map	Haz-Map2012
c) HPD	--
d) TOXMAP	TOXMAP2012
2) Akron database	Akron2012
3) SRI Directory of Chemical Producers	SRI2012
4) Chem Sources Suppliers	ChemSources2012a ChemSources2012b
5) National Health and Nutrition Examination Survey (NHANES) data studies	--
6) NIOSH National Occupational Exposure Survey (NOES) (1981-1983)	NIOSH1990
7) National Institute for Occupational Safety and Health (NIOSH) - Health Hazard Evaluations	NIOSH2012
8) National Response Center (NRC) Database	NRC2012
9) U.S. International Trade Commission (USITC) Interactive Tariff and Trade DataWeb	USITC2012
10) EPA Toxics Release Inventory (TRI)	TRI2012
11) Environmental Protection Agency (EPA) AP-42, Compilation of Air Pollutant Emission Factors	--
12) EPA EJView Database	EPA2013a-k
13) EPA High Production Volume Chemicals (HPV Challenge Program Chemical List) 1990-NF 1994-NF ADD-NF	--
14) EPA Inventory Update Rule (IUR) (Data for 1986, 1990, 1994, 1998, 2002, and 2006 combined in one file)	EPA2012
15) EPA Locating and Estimating (L&E) documents	--
16) EPA/Office of Pesticide Programs (OPP) Chemical Ingredients Database	--
17) Food and Drug Administration (FDA) Pesticide Monitoring Database	--
18) FDA Orange Book	--
19) FDA Total Diet Study	--
20) Medline Plus	--
21) United States Patent Office	--
22) Trademark Electronic Search System (TESS)	--
23) Material Safety Data Sheets (MSDS) (Multiple documents found; one each for *o*-toluidine and its HCl downloaded)	BASF2000 SigmaAldrich2001
24) Dow Chemical Product Safety Assessments	--

Table 4. Data sources for *ortho*-toluidine searches

Information type	Data sources
Synonyms	National Library of Medicine databases (e.g., ChemIDplus, Hazardous Substances Data Base)
Metabolites	Son *et al.* (1980)

Table 5. Literature search approach for *ortho*-toluidine

Substance	Search terms	Topics (combined with)[a]
ortho-Toluidine synonyms	o-toluidine, ortho-toluidine, 95-53-4, 2-toluidine, 1-amino-2-methylbenzene, 2-amino-1-methylbenzene, 2-aminotoluene, o-aminotoluene, ortho-aminotoluene, 2-methyl-1-aminobenzene, 2-methylaniline, o-methylaniline, ortho-methylaniline, o-methylbenzenamine, ortho-methylbenzenamine, 2-methylphenylamine, 2-tolylamine, o-tolylamine, ortho-tolylamine	Human exposure Toxicokinetics Human cancer studies Cancer studies in experimental animals Genotoxicity Toxicity Mechanism
ortho-Toluidine metabolites and their synonyms	Anthranilic acid, *N*-acetyl-anthranilic acid, *N*-acetyl-*o*-toluidine, *N*-acetyl-*o*-aminobenzyl alcohol, o-azoxytoluene, *o*-nitrosotoluene, *N*-hydroxy-*o*-toluidine, 4-amino-cresyl sulfate, *N*-acetyl-4-amino-*m*-cresyl sulfate, 2-amino-*m*-cresyl sulfate, 4-amino-*m*-cresyl glucuronide, 4-acetyl-4-amino-*m*-cresyl-glucuronide, *N*-acetyl-*o*-aminobenzyl glucuronide	Human cancer studies Cancer studies in experimental animals (for the mechanistic section) Genotoxicity Toxicity Mechanism
Chemical class synonyms	Monocyclic aromatic amines, arylamines, alkylanilines	Cancer studies in experimental animals (for the mechanistic section) Genotoxicity Toxicity Mechanism
Exposure scenarios (Dye industry, rubber chemical manufacturing, and herbicide manufacturing)	(dyestuff OR (dye AND (manufacturing OR manufacture)) OR rubber chemicals OR ortho toluidine OR o-toluidine OR chloro-o-toluidine OR chloro-*ortho* toluidine OR aniline OR ((manufacture OR manufacturing OR production) AND magenta) OR metolachlor OR acetochlor)	Human cancer studies

[a] Search terms for each of these topics were developed in consultation with an informational specialist.

Table 6. Search terms for monograph topics for *ortho*-toluidine

Monograph Topic	Search terms used in PubMed, Scopus, and Web of Science	MeSH terms used in Pubmed
Exposure	exposure OR occurrence OR oral OR dermal OR air OR water OR food OR soil OR environmental pollut* OR environmental exposure* OR occupational exposure*	("Environmental Pollutants" [MeSH] OR "Environmental Pollution" [MeSH])
ADME/ Toxicokinetics	*Toxicokinetic search terms*- administration OR absorption OR distribution OR tissue distribution OR bioavailab* OR biological availability OR metaboli* OR biotransform* OR activat* OR bioactivat* OR detoxif* OR excret* OR clearance OR eliminat* OR kinetic* OR pharmacokinetic* OR toxicokinetic* OR cytochrome P450 *Combine with AND* *Animal study search terms*- in vivo OR animal* OR mouse OR mice OR rat OR hamster OR guinea pig OR rabbit OR monkey OR dog	*Toxicokinetic search terms*- "Pharmacokinetics"[Mesh]) OR "Metabolism"[Mesh]) OR "Cytochrome P450 Enzyme System"[Mesh]
Human Cancer	(dyestuff OR (dye AND (manufacturing OR manufacture)) OR rubber chemicals OR ortho toluidine OR o-toluidine OR chloro-o-toluidine OR chloro-*ortho* toluidine OR aniline OR ((manufacture OR manufacturing OR production) AND magenta) OR metolachlor OR acetochlor) AND (cancer OR mortality OR follow-up OR incidence) AND (epidemiogic* OR workers OR case-control OR cohort OR case-report OR case-series))	None
Animal Tumors	*Cancer search terms*- cancer OR neoplasm* OR carcinogen* OR malignan* OR oncogene* OR tumor* OR tumour* *Combine with AND* *Animal study search terms*- animal* OR mouse OR mice OR rat OR hamster OR "guinea pig" OR rabbit OR monkey OR dog	*Cancer search terms*- "Neoplasms"[Mesh]) OR "Carcinogens"[Mesh]
Genotoxicity	genetic toxicology" OR clastogen* OR "DNA strand break*" OR "unscheduled DNA synthesis" OR "UDS" OR aneuploid OR aneuploid* OR polyploid OR polyploid* OR "neoplastic cell transformation" OR "chromosom* aberration*" OR cytogenetic OR cytogenetic* OR "DNA adduct*" OR "DNA damage" OR "DNA repair" OR crosslink* OR "germ-line mutation" OR micronucle* OR mutagen OR mutagen* OR mutation OR mutation* OR oncogen* OR "sister chromatid exchange" OR "SCE" OR "SOS response*" OR "Ames test" OR "gene expression" OR "cell proliferation" OR cytotoxic OR cytotoxic* OR	"DNA Damage"[Mesh] OR "DNA Repair"[Mesh] OR "Mutagens"[Mesh] OR "Mutation"[Mesh] OR "Cytogenetic Analysis"[Mesh] OR "Oncogenes"[Mesh] OR "Mutagenicity Tests"[Mesh]

Monograph Topic	Search terms used in PubMed, Scopus, and Web of Science	MeSH terms used in Pubmed
	"comet assay"	
Toxicity	toxic* OR toxin*OR cytotoxic* OR (nephrotoxic* OR hepatotoxic* OR pneumotoxic* OR thyrotoxic*	"Toxic Actions"[Mesh]) OR "Toxicity Tests"[Mesh]) OR "adverse effects" [Subheading]
Mechanisms of Carcinogenicity	((mode OR mechanism*) AND action) OR (carcinogen OR genetic OR epigenetic OR inhibit* OR promot* OR interact* OR activate* OR detoxific* OR "oxidative damage" OR alkylat* OR adduct)) AND ((animal OR animals OR mouse OR mice OR rat OR hamster OR "guinea pig" OR rabbit OR monkey OR dog OR pig) OR (person* OR people OR individual* OR subject* OR participant*))	

Part II. Updating the literature search

The literature searches will be updated prior to submitting the draft monograph for peer review and prior to finalizing the monograph. Monthly search alerts for *ortho*-toluidine synonyms, metabolites, chemical class, exposure scenarios (human cancer), and topic-focused searches were created in PubMed, Scopus, and Web of Science, and the results of these searches from the closing date of the initial search will be downloaded for review.

Part III. Review of citations using web-based systematic review software

Citations retrieved from literature searches were uploaded to web-based systematic review software and screened using inclusion and exclusion criteria. Multi-level reviews of the literature were conducted, with initial reviews (Level 1) based on titles and abstracts only to identify citations that could be excluded and to assign the included literature to one or more monograph topics; subsequent reviews (Level 2) for literature assigned to the various monograph topics (Exposure, ADME & TK, Human cancer studies, etc.) were based on full-text (i.e., PDFs) of the papers and were carried out by the writer and scientific reviewer for each monograph section. Two reviewers, at least one of whom is a member of the ORoC at NIEHS, participated at each level of review.

The questions based on inclusion/exclusion criteria for Levels 1 and 2 are listed below.

Inclusion/exclusion questions for literature

Level 1 (Primary screening using titles and abstracts):

Literature identified from searches in the major databases were categorized in one of three areas-

- ❍ 1) General Search (RefIDs 00001-20000)
- ❍ 2) Human Cancer Search (RefIDs 20001-40000)
- ❍ 3) Animal Tumors Search (RefIDs 40001-60000)

Note: In the context of the systematic review of literature used for *ortho*-toluidine, "relevant information" as it applies to primary screening can include any of the following:

- The article specifically mentions *ortho*-toluidine, a metabolite, or structural analogue and reports information on one of the topics included in a cancer evaluation (see the list of topics below)
- The article does not specifically mention *ortho*-toluidine or any related substance, but it does one of the following:
  - It reports information on one of the topics included in a cancer evaluation with potential for exposure to *ortho*-toluidine and should be included until full-text review, which would provide more information if the study is specific for exposure to *ortho*-toluidine or a related substance.
  - It reports information on an exposure scenario that could include exposure to *ortho*-toluidine.
  - It reports information on methodology that is potentially informative for evaluating cancer or mechanistic studies on exposure to *ortho*-toluidine.
  - It reports information on a potential mode of action that may be informative for *ortho*-toluidine.

General Search:
Should we obtain a pdf of this article because it appears to contain potentially relevant information for the review of *ortho*-toluidine?
❍ Yes

❍ No

Human Cancer Search:
Does this publication appear to contain information on potential exposure to *ortho*-toluidine (including exposure inferred from knowledge of an exposure scenario) and human cancer? Relevant information includes, but is not limited to, epidemiologic studies, descriptive studies, pooled analyses, meta-analyses, reviews, letters to editors, exposure-assessment studies (for use in epidemiologic studies) and information on co-exposures or potential confounders and other special topics of relevance to the evaluation.
❍ Yes
❍ No

Cancer in Experimental Animals Search:
Does this paper contain information on exposure of animals to *ortho*-toluidine (or to a metabolite, structural analogue, or member of the same chemical class) and the incidence or tumors of the potential for tumor formation (including negative results)?
❍ Yes
❍ No

When "Yes" is selected for any of the questions above, the question below is addressed next:

For which sections of the monograph does the article contain useful information? Check all that apply.

☐ Properties and Human Exposure
☐ Toxicokinetics (also includes ADME, i.e., absorption, distribution, metabolism, and excretion)
☐ Human Cancer Studies
☐ Studies of Cancer in Experimental Animals
☐ Mechanisms- Genetic Toxicology
☐ Mechanisms- Toxicity
☐ Mechanisms of Carcinogenicity

When "No" is selected for any of the questions above, the next step depends on the category (i.e., general, human, or animal searches).

General Search:
Check the reason below that explains the exclusion of this study from further consideration.
❍ It does not contain relevant information on the candidate substance or any related substance (metabolite, structural analogue, or member of the same chemical class).
❍ It contains information relevant to the candidate substance or a related substance (metabolite, structural analogue, or member of the same chemical class), but it does not contain information relevant to any topic covered by the monograph.
❍ Other. (Enter response in text box.)

Human Cancer Search:
If the response to Question 1 is "No," identify all reasons that apply from the list below for excluding this publication from the Human Cancer section.
❍ Potential exposure to *ortho*-toluidine is not likely in this study.
❍ Potential exposure to *ortho*-toluidine is likely but the study is not a study in humans or related to an issue relevant to interpreting epidemiologic data.
❍ Other. (Enter response in text box.)

Cancer in Experimental Animals Search:
Check the reason below that explains the exclusion of this study from further consideration.
❍ It does not contain relevant information on the candidate substance or any related substance (metabolite, structural analogue, or member of the same chemical class).
❍ It contains information relevant to the candidate substance or a related substance (metabolite, structural analogue, or member of the same chemical class), but it does not contain information relevant to any topic covered by the monograph.
❍ Other. (Enter response in text box.)

Level 2 (Full text review):

Note: Level 2 reviews exist for all major topics in the monograph, i.e., (1) Exposure, (2) Toxicokinetics (including ADME), (3) Human cancer studies, (4) Animal tumor studies, (5) Genetic toxicology, (6) Toxicity, and (7) Mechanisms of Action. The reviewers for Level 2 topics are asked to consider the following question for all papers:

If this paper could have useful information for any additional sections of the monograph based on your review of the PDF, indicate those additional sections below.
☐ Properties and Human Exposure
☐ Toxicokinetics (also includes ADME, i.e., absorption, distribution, metabolism, and excretion)
☐ Human Cancer Studies
☐ Studies of Cancer in Experimental Animals
☐ Mechanisms- Genetic Toxicology
☐ Mechanisms- Toxicity
☐ Mechanisms of Carcinogenicity

Exposure

1. Does this paper contain information that could be useful in answering the key questions about exposure?
   ❍ Yes
   ❍ No

2. If the answer to Question #1 is "No," select the reason below for excluding it from review.
   ❍ It does not contain relevant information on the candidate substance (or one of its metabolites or analogues.
   ❍ It is related to the candidate substance (or one of its metabolites or analogues), but the paper does not contain information that will help answer the key questions about exposure.
   ❍ Other. (Enter response in text box.)

Note: In the context of the systematic review of literature used for *ortho*-toluidine, "useful information" as it applies to screening for the exposure section can include information, from either primary research papers, review articles, databases, or other published sources, on any of the following topics: occupational exposure, environmental occurrence, occurrence in consumer products, food, cigarette smoke, or other sources, biological indices of exposure, and Federal regulations or guidelines to reduce exposure.

Toxicokinetics (including Absorption, Distribution, Metabolism, and Excretion)

1. Does this paper contain information that could be useful in answering the key questions about toxicokinetics?
   ❍ Yes
   ❍ No

2. If the answer to Question #1 is "No," select the reason below for excluding it from review.
   ❍ It does not contain relevant information on the candidate substance (or one of its metabolites or analogues.
   ❍ It is related to the candidate substance (or one of its metabolites or analogues), but the paper does not contain information that will help answer the key questions about toxicokinetics.
   ❍ Other. (Enter response in text box.)

Note: In the context of the systematic review of literature used for *ortho*-toluidine, "useful information" as it applies to screening for the toxicokinetics (and ADME) section can include (but is not limited to) information from primary research papers or review articles on any of the following topics: absorption, distribution, metabolism, excretion (ADME), toxicokinetics, and physiologically based pharmacokinetic models (PBPK).

Human Cancer

(1) Does this publication contain relevant information (as defined above) on potential exposure to *ortho*-toluidine (including exposure inferred from knowledge of an exposure scenario) and human cancer?

   ❍ Yes

   ❍ No

(2) If the response to Question 1 is "No," identify all reasons that apply from the list below for excluding this publication from the Human Cancer section.

❍ (a) No information is provided on potential exposure to *ortho*-toluidine in this study.

❍ (b) Potential exposure to *ortho*-toluidine is likely in the study or is mentioned in the review or publication, but the publication is not one of the following:

(i) an epidemiologic study (such as cohort, case-control, ecological, pooled, meta-analysis) or descriptive study (such as case report or case-series) that provides information on human cancer.

(ii) a review, letter to the editor, or abstract, or other type of study provided relevant information related to *ortho*-toluidine and human cancer.

(iii) a study or other source of data that provides information, such as on exposure assessment, relevant to evaluating the epidemiologic studies.

❍ (c) The publication does not provide information on co-exposures or potential confounders or other special topic(s) relevant to the evaluation.

Note: In the context of the systematic review of literature used for *ortho*-toluidine, "useful information" as it applies to screening for the human cancer section can include, but is not limited to, epidemiologic studies, descriptive studies, pooled analyses, meta-analyses, case reports, reviews, letters to editors, exposure-assessment studies (for use in epidemiologic studies) and information on co-exposures or potential confounders and other special topics of relevance to the evaluation.

Animal Tumors

1. Does this paper contain information that could be useful in answering the key questions about animal tumors?
   ❍ Yes
   ❍ No

2. If the answer to Question #1 is "No," select the reason below for excluding it from review.
   ❍ It does not contain relevant information on the candidate substance (or one of its metabolites or analogues.
   ❍ It is related to the candidate substance (or one of its metabolites or analogues), but the paper does not contain information that will help answer the key questions about animal tumors.
   ❍ Other. (Enter response in text box.)

Note: In the context of the systematic review of literature used for *ortho*-toluidine, "useful information" as it applies to screening for the animal tumors section can include, but is not limited to, information from primary research papers or review articles on (1) chronic studies (ideally for the lifetime of the animal) in experimental animals that are assessing neoplastic endpoints, non-cancer data important for cancer assessment, such as

preneoplastic lesions that are considered part of a morphologic continuum to neoplasia, or (2) subchronic studies in experimental animals that provide information on preneoplastic lesions, neoplastic lesions, or on dose setting for chronic studies.

Genetic Toxicology

3. Does this paper contain information that could be useful in answering the key questions about genetic toxicology?
   - ❍ Yes
   - ❍ No

4. If the answer to Question #1 is "No," select the reason below for excluding it from review.
   - ❍ It does not contain relevant information on the candidate substance (or one of its metabolites or analogues).
   - ❍ It is related to the candidate substance (or one of its metabolites or analogues), but the paper does not contain information that will help answer the key questions about genetic toxicology.
   - ❍ Other. (Enter response in text box.)

Note: In the context of the systematic review of literature used for *ortho*-toluidine, "useful information" as it applies to screening for the genetic toxicology section can include information from primary research papers or review articles on studies in experimental systems (both *in vitro* and *in vivo*) and in exposed humans assessing the following endpoints: both direct and indirect DNA or chromosomal damage, events associated with mutagenesis, cellular transformation or other related effects.

Toxicity

5. Does this paper contain information that could be useful in answering the key questions about toxicity?
   - ❍ Yes
   - ❍ No

6. If the answer to Question #1 is "No," select the reason below for excluding it from review.
   - ❍ It does not contain relevant information on the candidate substance (or one of its metabolites or analogues.
   - ❍ It is related to the candidate substance (or one of its metabolites or analogues), but the paper does not contain information that will help answer the key questions about toxicity.
   - ❍ Other. (Enter response in text box.)

Note: In the context of the systematic review of literature used for *ortho*-toluidine, "useful information" as it applies to screening for the toxicity section can include any of

the following: information from primary research papers or review articles on the toxicity of *ortho*-toluidine to organs or tissues that were identified as tumor sites from studies in experimental animals.

Mechanistic data

7. Does this paper contain information that could be useful in answering the key questions about mechanistic data?
   ❍ Yes
   ❍ No

8. If the answer to Question #1 is "No," select the reason below for excluding it from review.
   ❍ It does not contain relevant information on the candidate substance (or one of its metabolites or analogues.
   ❍ It is related to the candidate substance (or one of its metabolites or analogues), but the paper does not contain information that will help answer the key questions about mechanistic data.
   ❍ Other. (Enter response in text box.)

Note: In the context of the systematic review of literature used for *ortho*-toluidine, "useful information", as it applies to screening for the mechanistic data section, can include information from primary research papers or review articles on data related to molecular alterations associated with carcinogenicity or potential modes of action, such as genotoxicity, epigenetics, gene expression, immune-response modulation, inflammation, cytotoxicity and compensatory cell proliferation, mitogenicity, chronic metabolic or physiologic overload, nutrient deficiency, and interference with intercellular communication, for *ortho*-toluidine, its metabolites and analogues.

1. Level 3 (Selection of primary epidemiologic studies):

Primary literature used in the human cancer evaluation was selected from the Level 2-selected references that met the criteria listed below in Questions 1 to 3. Analytical studies (such as case-control studies, cross-sectional studies, cohort studies or pooled analyses) in which potential exposure to *ortho*-toluidine can be established by quantitative or qualitative exposure assessment, by the authors' report, or reliably inferred using relevant knowledge of industrial processes, were considered for the full cancer evaluation. Technical assistance from experts in dye and rubber chemical manufacturing processes has been used to establish the likelihood of potential exposure to *ortho*-toluidine (including relative levels) and co-exposures over time in studies where qualitative or quantitative exposure data are not available. In the majority of cohort or case-control studies, subjects are typically exposed to multiple chemical agents in addition to the substance of concern. In certain studies, where the predominant exposure is to another suspect or known carcinogen and where the levels of *ortho*-toluidine are low or unknown, it was not possible to evaluate the possibility of an independent association

(or effect modification) between observed cancers and exposure to *ortho*-toluidine. In such cases, studies have been excluded from the full cancer evaluation.

Primary epidemiologic studies (such as descriptive studies) on potential exposure to *ortho*-toluidine that were retrieved from the literature search strategy and not included in the cancer evaluation, and the reason for their exclusion, are identified in the monograph. Information from multiple publications relating to the same study population may be included in the draft monograph, but the publications are counted as one study.

Exclusion/inclusion questions

Is the publication a peer-reviewed, primary research study on potential exposure to ortho-*toluidine and human cancer?*

- ❑ Yes
- ❑ No

(3) If the answer to question 1 is yes, does the study report a risk estimate (or information to calculate a risk estimate) for cancer?

- ❑ Yes
- ❑ No

(4) Are there exposure analyses specific for ortho-*toluidine? If not, is there evidence that exposure to* ortho-*toluidine is likely to be substantial or predominant in relation to exposure to known or suspect carcinogenic co-exposures?*

- ❑ Yes
- ❑ No

Part IV. General searches for potential confounders

The following potential confounders were identified from human epidemiologic studies summarized in Section 3 and Appendix D:

ortho-Nitrotoluene
4,4'-Methylene bis(2-methylaniline)
ortho-Aminoazotoluene
Aniline
4-Chloro-*ortho*-toluidine
Nitrobenzene
Hydroquinone
N-Phenyl-2-naphthylamine (phenyl-β-naphthylamine)
2-Mercaptobenzothiazole

The general sources of information, e.g., NTP technical reports, IARC monographs, or ATSDR toxicological profiles, were searched for each of these substances and the results are summarized in Table 7a-i below for each substance.

Table 7a. General sources checklist for: _____*ortho*-Nitrotoluene_____

Source	Name of document
1) NTP technical reports	NTP2002 (TR-504) NTP1996 (TOX-44)
2) NTP nomination for toxicological evaluation documents	Nominated 5/8/84 (No Document)
3) NTP RoC Background Documents	NTP2008
4) NTP RoC Profiles	NTP2011
5) OHAT (formerly CERHR)	--
6) IARC monographs	IARC1996 IARC2012
7) ATSDR Toxicological Profiles	--
8) EPA IRIS	--
9) WHO (IPCS) INCHEM-related documents (a-k below)	
a) CICADS	--
b) EHC	--
c) HSGs	--
d) ICSCs	IPCS2000
e) JECFA	--
f) JMPR	--
g) KemI-Riskline	--
h) PDs	--
i) PIMS	--
j) SIDS	--
k) UKPID	--
10) California EPA Prop 65 hazard identification documents	Listed 1998 (No Document)

Table 7b. General sources checklist for: 4,4'-methylene bis(2-methylaniline

Source	Name of document
1) NTP technical reports	--
2) NTP nomination for toxicological evaluation documents	--
3) NTP RoC Background Documents	--
4) NTP RoC Profiles	--
5) OHAT (formerly CERHR)	--
6) IARC monographs	IARC1974 IARC1987
7) ATSDR Toxicological Profiles	--
8) EPA IRIS	--
9) WHO (IPCS) INCHEM-related documents (a-k below)	
a) CICADS	--
b) EHC	--
c) HSGs	--
d) ICSCs	--
e) JECFA	--
f) JMPR	--
g) KemI-Riskline	--
h) PDs	--
i) PIMS	--
j) SIDS	--
k) UKPID	--
10) California EPA Prop 65 hazard identification documents	Listed 1998 (No Document)

Table 7c. General sources checklist for: ortho-Aminoazotoluene

Source	Name of document
1) NTP technical reports	--
2) NTP nomination for toxicological evaluation documents	Nominated 9/2/87 (No Document)
3) NTP RoC Background Documents	--
4) NTP RoC Profiles	NTP2011
5) OHAT (formerly CERHR)	--
6) IARC monographs	IARC1975
7) ATSDR Toxicological Profiles	--
8) EPA IRIS	--
9) WHO (IPCS) INCHEM-related documents (a-k below)	
a) CICADS	--
b) EHC	--
c) HSGs	--
d) ICSCs	--
e) JECFA	--
f) JMPR	--
g) KemI-Riskline	--
h) PDs	--
i) PIMS	--
j) SIDS	--
k) UKPID	--
10) California EPA Prop 65 hazard identification documents	Listed 1987 (No Document)

Table 7d. General sources checklist for: Aniline

Source	Name of document
1) NTP technical reports	NTP1978 (TR-130, Aniline HCl)
2) NTP nomination for toxicological evaluation documents	Nominated 7/11/74 (No Document)
3) NTP RoC Background Documents	--
4) NTP RoC Profiles	--
5) OHAT (formerly CERHR)	--
6) IARC monographs	IARC1974 IARC1982 IARC1987
7) ATSDR Toxicological Profiles	--
8) EPA IRIS	EPA1990 EPA1994
9) WHO (IPCS) INCHEM-related documents (a-k below)	
a) CICADS	--
b) EHC	--
c) HSGs	--
d) ICSCs	IPCS2001a,b (Aniline & Aniline HCl)
e) JECFA	--
f) JMPR	--
g) KemI-Riskline	--
h) PDs	--
i) PIMS	--
j) SIDS	--
k) UKPID	--
10) California EPA Prop 65 hazard identification documents	Listed 1990 and 1998 (HCl) OEHHA1997

Table 7e. General sources checklist for: 4-Chloro-*ortho*-Toluidine

Source	Name of document
1) NTP technical reports	NTP1979 (TR-165, HCl)
2) NTP nomination for toxicological evaluation documents	--
3) NTP RoC Background Documents	NTP1999
4) NTP RoC Profiles	NTP2011
5) OHAT (formerly CERHR)	--
6) IARC monographs	IARC1978 IARC1990 IARC2000 IARC2010
7) ATSDR Toxicological Profiles	--
8) EPA IRIS	--
9) WHO (IPCS) INCHEM-related documents (a-k below)	
a) CICADS	--
b) EHC	--
c) HSGs	--
d) ICSCs	--
e) JECFA	--
f) JMPR	--
g) KemI-Riskline	--
h) PDs	--
i) PIMS	--
j) SIDS	--
k) UKPID	--
10) California EPA Prop 65 hazard identification documents	Listed 1990 OEHHA2002

Table 7f. General sources checklist for: Nitrobenzene

Source	Name of document
1) NTP technical reports	--
2) NTP nomination for toxicological evaluation documents	Nominated 1/79 (No Document)
3) NTP RoC Background Documents	NTP2002
4) NTP RoC Profiles	NTP2011
5) OHAT (formerly CERHR)	V
6) IARC monographs	IARC1996
7) ATSDR Toxicological Profiles	ATSDR1990
8) EPA IRIS	EPA2009a,b,c
9) WHO (IPCS) INCHEM-related documents (a-k below)	
a) CICADS	--
b) EHC	WHO2003
c) HSGs	--
d) ICSCs	IPCS2006
e) JECFA	--
f) JMPR	--
g) KemI-Riskline	--
h) PDs	--
i) PIMS	--
j) SIDS	--
k) UKPID	--
10) California EPA Prop 65 hazard identification documents	Listed 1997 (No Document)

Table 7g. General sources checklist for: Hydroquinone

Source	Name of document
1) NTP technical reports	NTP1989 (TR-366)
2) NTP nomination for toxicological evaluation documents	Nominated 6/10/09 NTP2009 Nominated 1/79 (No Document)
3) NTP RoC Background Documents	--
4) NTP RoC Profiles	--
5) OHAT (formerly CERHR)	--
6) IARC monographs	IARC1977 IARC1999
7) ATSDR Toxicological Profiles	--
8) EPA IRIS	EPA1990a,b
9) WHO (IPCS) INCHEM-related documents (a-k below)	
a) CICADS	--
b) EHC	WHO1994
c) HSGs	WHO1996
d) ICSCs	IPCS2001
e) JECFA	--
f) JMPR	--
g) KemI-Riskline	--
h) PDs	--
i) PIMS	--
j) SIDS	UNEP1996
k) UKPID	--
10) California EPA Prop 65 hazard identification documents	--

Table 7h. General sources checklist for: N-Phenyl-2-naphthylamine (phenyl-β-naphthylamine)

Source	Name of document
1) NTP technical reports	NTP1988 (TR-333)
2) NTP nomination for toxicological evaluation documents	Nominated 4/77 (No Document)
3) NTP RoC Background Documents	--
4) NTP RoC Profiles	--
5) OHAT (formerly CERHR)	--
6) IARC monographs	IARC1978 IARC1987
7) ATSDR Toxicological Profiles	--
8) EPA IRIS	--
9) WHO (IPCS) INCHEM-related documents (a-k below)	
a) CICADS	--
b) EHC	--
c) HSGs	--
d) ICSCs	IPCS2003
e) JECFA	--
f) JMPR	--
g) KemI-Riskline	--
h) PDs	--
i) PIMS	--
j) SIDS	--
k) UKPID	--
10) California EPA Prop 65 hazard identification documents	--

Table 7i. General sources checklist for: 2-Mercaptobenzothiazole

Source	Name of document
1) NTP technical reports	NTP1988 (TR-332)
2) NTP nomination for toxicological evaluation documents	Nominated 1/79 (No Document)
3) NTP RoC Background Documents	--
4) NTP RoC Profiles	--
5) OHAT (formerly CERHR)	--
6) IARC monographs	--
7) ATSDR Toxicological Profiles	--
8) EPA IRIS	--
9) WHO (IPCS) INCHEM-related documents (a-k below)	
a) CICADS	--
b) EHC	--
c) HSGs	--
d) ICSCs	IPCS2004
e) JECFA	--
f) JMPR	--
g) KemI-Riskline	--
h) PDs	--
i) PIMS	--
j) SIDS	--
k) UKPID	--
10) California EPA Prop 65 hazard identification documents	--

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