

EPA's Safer Choice Criteria for Solvents



1 Introduction

To identify safer solvents, EPA Safer Choice focuses on the characteristics (hazard endpoints) that are relevant to solvents and that distinguish safer solvents from those of greater concern. With solvents, in general, there are potential concerns for the following endpoints: carcinogenicity, acute mammalian toxicity, reproductive and developmental toxicity, repeated-dose toxicity, neurotoxicity, and environmental fate and toxicity. These are termed the “Attributes of Concern.” For the four classes of the Phase I Solvents (alcohols, esters, ethylene glycol ethers, and propylene glycol ethers), the distinguishing hazard endpoints, which are a subset of the Attributes of Concern, are: acute mammalian toxicity, reproductive and developmental toxicity, repeated-dose toxicity, and environmental fate and toxicity. These are termed the “Distinguishing Attributes of Concern.”

Safer Choice has selected the Distinguishing Attributes of Concern based on their ability to differentiate safer from less safe solvents and on the availability or feasibility of generating data to address these endpoints. In applying the screen, Safer Choice will seek data on all Attributes of Concern; data on any single attribute that does not meet the Safer Choice threshold for a safer solvent will cause the solvent to fail the screen. For a solvent to pass the screen, all available data must satisfy these thresholds and, very importantly, there must be data on all distinguishing attributes—either on the chemical itself or a close analog—indicating that the solvent meets safety thresholds. (Phase II Solvents—amides, amines, and terpenes—may have different Distinguishing Attributes of Concern.)

Table 1 – Safer Choice Criteria for Solvents (Phase I)

Phase I Solvent Classes	Alcohols
	Esters
	Ethylene Glycol Ethers (EGEs)
	Propylene Glycol Ethers (PGEs)
Attributes of Concern for Phase I Solvents	Carcinogenicity
	Neurotoxicity
	Acute Mammalian Toxicity
	Reproductive and Developmental Toxicity
	Repeated-Dose Toxicity
	Environmental Fate and Toxicity

2 Terms

2.1 Alcohol: An organic compound containing at least one hydroxyl group (OH). Compounds having two hydroxyl groups are referred to as “diols”. Alcohols can be primary (1°), secondary (2°) or tertiary (3°), depending on the position at which they are attached and the degree of branching of the molecule.

2.2 Dust: Solid particles of a material suspended in a gas, usually air [1].

2.3 Esters: The condensation product of an alcohol with a carboxylic acid. Cyclic esters (lactones) are not included in this definition and should not be reviewed using this screen because they are generally unsuitable for use as solvents.

2.4 Ethylene glycol ethers (EGEs): Monoethers of mono- and di-ethylene glycol, and their corresponding acetate esters; glyme and diglyme.

$R-(OCH_2CH_2)_nOH$, and acetate esters $Me-(OCH_2CH_2)_nOMe$
Where R = branched or linear C1-C7 alkyl.

2.5 LOAEL: Lowest Observed Adverse Effect Level

2.6 Mist: Liquid droplets of a substance or mixture suspended in a gas, usually air [1].

2.7 NOAEL: No Observed Adverse Effect Level

2.8 Propylene glycol ethers (PGEs): This class includes mono- and di- ethers of 1,2-propanediol (propylene glycol), 1-[2-hydroxy(methylethoxy)]-2-propanol (dipropylene glycol) and 1,2-bis[2-hydroxy(methylethoxy)]propane (tripropylene glycol), and their corresponding acetate esters.

$R-(OCH_2CH_2CH_2)_nOH$, and acetate esters $Me-(OCH_2CH_2CH_2)_nOMe$
Where R = branched or linear C1-C7 alkyl.

2.9 Vapor: The gaseous form of a substance or mixture released from its liquid or solid state [1].

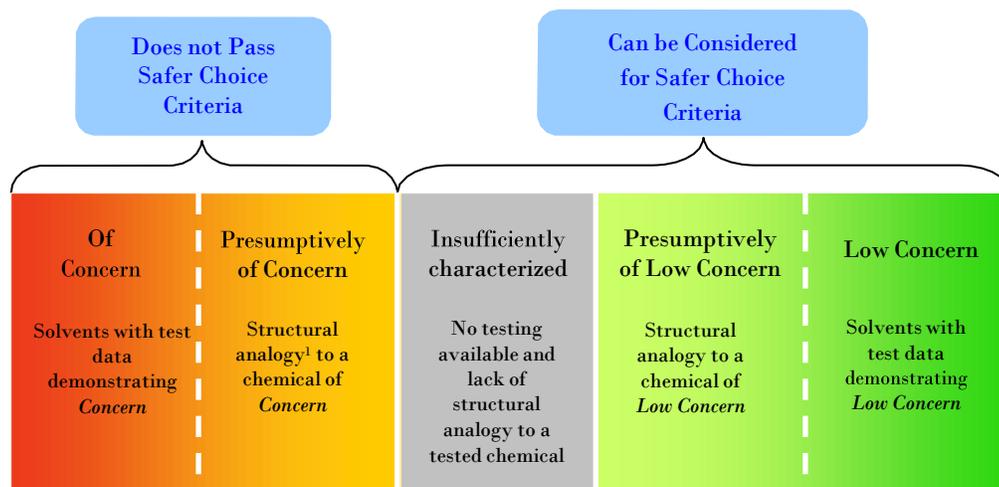
3 Preferences

The following preferences and terms apply to all attributes and data requirements.

- 3.1** Every solvent must be screened individually. It is not expected that all solvents from these four classes will pass the screen.
- 3.2** Data for all available routes of exposure will be evaluated. Failure to pass an endpoint by any route of exposure results in failure to pass the screen.
- 3.3** Test data using dermal and inhalation exposure routes are preferred over oral exposure data because the former are more likely routes of exposure.
- 3.4** The GHS criteria and data evaluation approach, and EPA risk assessment guidance, will inform professional judgment in the review of both no observed adverse effect levels/concentrations (NOAEL/NOAEC) and lowest observed adverse effect levels/concentrations (LOAEL/LOAEC). NOAEL/NOAEC and LOAEL/LOAEC values are preferred to no observed effect levels/concentrations (NOEL/NOECs) and lowest observed effect levels/concentrations (LOEL/LOECs).
- 3.5** The definitions in Section 2 shall apply in all cases.
- 3.6** Use of existing data should follow the EPA HPV Challenge Program's data adequacy guidelines[2].

4 Attributes of Concern for all Solvents

Fully characterized endpoints for all chemicals are optimal. However, insufficient characterization may be acceptable for the endpoints of carcinogenicity and neurotoxicity, because concern is not expected and data are limited, respectively. Data or valid analogs will be reviewed whenever they are available (see Figure 1 below).



¹Can also include metabolic or mechanistic analogy.

Figure 1 – A diagrammatic representation of the continuum from high concern to low concern and data requirements for screening qualification for carcinogenicity and neurotoxicity.

4.1 CARCINOGENICITY

4.1.1 Criteria

Phase I Solvents will be screened for carcinogenicity based upon established lists and GHS criteria (see Table 2).

4.1.2 Data Evaluation

Available data on the solvent or valid analog along with the OncoLogic™ [3] model will be used to assess a solvent under GHS.

Table 2 – Carcinogenicity

Authoritative Body	Does not pass Safer Choice Criteria
International Agency for Research on Cancer (IARC)	Group 1 – carcinogenic to humans Group 2A – probably carcinogenic to humans Group 2B – possibly carcinogenic to humans
National Toxicology Program (NTP)	Known to Be Human Carcinogen Reasonably Anticipated to Be Human Carcinogen
U.S. Environmental Protection Agency (EPA)	(2005/1999) “Carcinogenic to humans”, “Likely to be carcinogenic to humans”, or “Suggestive evidence of carcinogenic potential” (1996) “Known/Likely” (1986) “Group A – Human Carcinogen”, “Group B – Probable human carcinogen,” or “Group C – Possible human carcinogen”
Globally Harmonized System (GHS) [4]	Category 1 – Known or presumed human carcinogens ¹ Category 2 – Suspected human carcinogens ¹
¹ For chemicals where available carcinogenicity data have not been reviewed by IARC, NTP, or EPA	

4.1.3 Preferred Test Methods

- OECD Test Guideline 451: Carcinogenicity Studies [5];
- OECD Test Guideline 453: Combined Chronic Toxicity/Carcinogenicity Studies [6];
- OPPTS Harmonized Guideline 870.4200: Carcinogenicity [7];
- OPPTS Harmonized Guideline 870.4300: Combined Chronic Toxicity/Carcinogenicity [8];
- NTP 2 Year Study Protocol: “Specifications for the conduct of studies to evaluate the toxic and carcinogenic potential of chemical, biological and physical agents in laboratory animals for the National Toxicology Program” [9].

4.1.4 Data Interpretation

4.1.4.1 Section 2, Hazard Assessment in *Guidelines for Carcinogen Risk Assessment* [10]

4.1.4.2 GHS Ch 3.6 Carcinogenicity [4]

4.2 NEUROTOXICITY

4.2.1 Criteria

No solvents that are classifiable as neurotoxicants according to GHS [4] (see guidance values in Table 3) will pass the screen for this endpoint. Insufficiently characterized solvents may be considered for the Safer Choice Criteria.

4.2.2 Data Evaluation

Available data on the solvent or valid analog will be used to assess a solvent under GHS.

Table 3 - Neurotoxicity

Route of Exposure	Guidance values ¹
Oral (mg/kg-bw/day)	> 100
Dermal (mg/kg-bw/day)	>200
Inhalation (gas) (ppm/6h/day)	>250
Inhalation (vapor) (mg/L/6h/day)	>1.0
Inhalation (dust/mist) (mg/L/6h/day)	>0.2

¹The doses provided are for 90-day studies. Guidance values are tripled for chemicals evaluated in 28-day studies.

4.2.3 Preferred Test Methods

- OECD Test Guideline 424: Neurotoxicity Study in Rodents [11] and
- OPPTS Harmonized Guideline 870.6200: Neurotoxicity screening battery [12].

4.2.4 Optional Test Methods

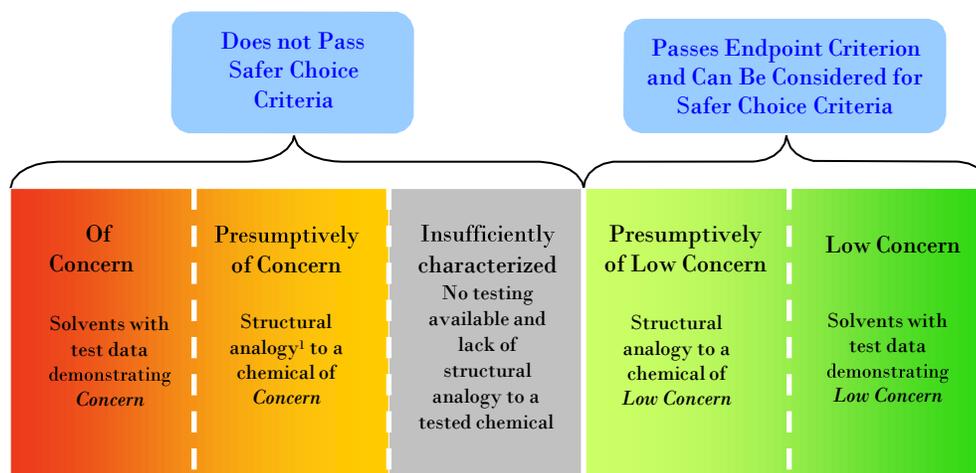
Additional evidence from OECD Test Guideline 426: Developmental Neurotoxicity Study [13] and OPPTS Harmonized Guideline: 870.6300 Developmental neurotoxicity study [14] can be used to screen solvents for neurotoxicity.

4.2.5 Data Interpretation

- Section 3, Hazard Characterization in *Guidelines for Neurotoxicity Risk Assessment* [15]
- GHS Ch. 3.9 Specific Target Organ Toxicity Repeated Exposure [16]

5 Distinguishing Attributes of Concern

Insufficient characterization is not acceptable for the endpoints listed below. Test data are acceptable and data from analogous chemicals may be acceptable (see Figure 2.)



¹Can also include metabolic or mechanistic analogy.

Figure 2 - A diagrammatic representation of the continuum from high concern to low concern and data requirements for screening qualification for acute toxicity, PBT, reproductive and developmental toxicity and repeated dose toxicity.

5.1 ACUTE MAMMALIAN TOXICITY

5.1.1 Criteria

To be acceptable under the screen, Phase I Solvents must have a median lethal dose or concentration greater than those values listed in Table 4.

5.1.2 Data Evaluation

Data must be available for at least one route of exposure. For inhalation, exposure must be at least four hours; the thresholds for inhalation are the same for exposures greater than four hours. Exposures of less than four hours will be evaluated on a case-by-case basis. Data for all available routes of exposure will be evaluated. Failure to pass this endpoint by any route of exposure results in failure to pass the screen.

Table 4 Acute Mammalian Toxicity

Route of Exposure	Median Lethal Dose/Concentration
Oral LD50 (mg/kg)	>2000
Dermal LD50 (mg/kg)	>2000
Inhalation LC50 (gas) (ppm)	>5000
Inhalation LC50 (vapor) (mg/L)	>20
Inhalation LC50 (dust/mist) (mg/L)	>5

5.1.3 Test Methods

- OPPTS Harmonized Guideline: 870.1100 Acute oral toxicity [17];
- OPPTS Harmonized Guideline: 870.1200 Acute dermal toxicity [18];
- OPPTS Harmonized Guideline: 870.1300 Acute inhalation toxicity [19];
- OECD Test Guideline 420: Acute Oral Toxicity – Fixed Dose Method [20];
- OECD Test Guideline 423: Acute Oral Toxicity – Acute Toxic Class Method [21];
- OECD Test Guideline 425: Acute Oral Toxicity – Up-and-Down Procedure [22];
- OECD Test Guideline 402: Acute Dermal Toxicity [23]; and
- OECD Test Guideline 403: Acute Inhalation Toxicity [24].

5.2 REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

5.2.1 Criteria

Phase I Solvents will not be acceptable under the screen if they are classifiable as reproductive toxicants according to GHS [25] (see guidance values in Table 5). Following the SIDS Dossier [26], all solvents must be reviewed for both fertility and developmental effects.

5.2.2 Data Evaluation

Data on reproductive and developmental toxicity must be available via at least one of the routes of exposure below. Data for all available routes of exposure will be evaluated. Failure to pass this endpoint by any route of exposure or toxicity effect (fertility or development) results in failure to pass the screen.

Table 5 – Reproductive and Developmental Toxicity

Route of Exposure	Guidance Values
Oral (mg/kg-bw/day)	>250
Dermal (mg/kg-bw/day)	>200
Inhalation (gas) (ppm/6h/day)	>250
Inhalation (vapor) (mg/L/6h/day)	>1.0
Inhalation (dust/mist) (mg/L/6h/day)	>0.2

5.2.3 Test Methods

5.2.3.1 Fertility test methods, preferred

- OECD Test Guideline 415: One-Generation Reproduction Toxicity Study [27] and
- OECD Test Guideline 416: Two-Generation Reproduction Toxicity Study [28].

5.2.3.2 Fertility test methods, acceptable

- OPPTS 870.3800: Reproduction and fertility effects [29]

The following test methods may be used to justify classification, per GHS [25]:

- OECD Test Guideline 421: Reproduction/Developmental Toxicity Screening Test [30]
- OECD Test Guideline 422: Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test [31]
- OPPTS Harmonized Guideline 870.3550: Reproduction/developmental toxicity screening test [32]
- OPPTS Harmonized Guideline 870.3650: Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test [33]

5.2.3.3 Developmental toxicity test methods, preferred

- OECD Test Guideline 414: Prenatal Developmental Toxicity Study [34].

5.2.3.4 Developmental toxicity test methods, acceptable

- OPPTS 870.3700: Prenatal developmental toxicity study [35]

The following test methods may be used to justify classification, per GHS [25]:

- OECD Test Guideline 421: Reproduction/Developmental Toxicity Screening Test [30]
- OECD Test Guideline 422: Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test [31]
- OPPTS Harmonized Guideline 870.3550: Reproduction/developmental toxicity screening test [32]
- OPPTS Harmonized Guideline 870.3650: Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test [33]

5.2.4 Data Interpretation

- Section 3, Hazard Characterization, *Guidelines for Reproductive Toxicity Risk Assessment* [36]
- Section 3, Hazard Characterization, *Guidelines for Developmental Toxicity Risk Assessment* [37]
- GHS Ch 3.7 Reproductive Toxicity [25]

5.3 REPEATED-DOSE TOXICITY

5.3.1 Criteria

Phase I Solvents will not be acceptable under the screen if they are classifiable as systemic toxicants according to GHS [16] (see guidance values in Table 6).

Table 6 – Repeated-Dose Toxicity

Route of Exposure	Guidance values ¹
Oral (mg/kg-bw/day)	>100
Dermal (mg/kg-bw/day)	>200
Inhalation (gas) (ppm/6h/day)	>250
Inhalation (vapor) (mg/L/6h/day)	>1.0
Inhalation (dust/mist/fume) (mg/L/6h/day)	>0.2

¹The doses provided are for 90-day studies. Guidance values are tripled for chemicals evaluated in 28-day studies and similarly modified for studies of longer durations.

5.3.2 Data Evaluation

Data must be available for at least one of the above routes of exposure, although inhalation and dermal exposure data are preferred. Data for all available routes of exposure will be evaluated, and any study must be 28 days or greater to satisfy this endpoint. Should testing be pursued to meet the screen data requirement, a functional observational battery (FOB) should be added to the test method to provide neurotoxicity information.

5.3.3 Preferred Test Methods

- OECD Test Guideline 408: Repeated Dose 90-Day Oral Toxicity Study in Rodents [38]
- OECD Test Guideline 409: Repeated Dose 90-Day Oral Toxicity Study in Non-Rodents [39]
- OECD Test Guideline 411: Subchronic Dermal Toxicity: 90-day Study [40]
- OECD Test Guideline 413: Subchronic Inhalation Toxicity: 90-day Study [41]
- OPPTS Harmonized Guideline 870.3100: 90-Day oral toxicity in rodents [42]
- OPPTS Harmonized Guideline 870.3150: 90-Day oral toxicity in nonrodents [43]
- OPPTS Harmonized Guideline 870.3250: 90-Day dermal toxicity [44]
- OPPTS Harmonized Guideline 870.3465: 90-Day inhalation toxicity [45]

5.3.4 Acceptable Test Methods

- OECD Test Guideline 412: Repeated Dose Inhalation Toxicity: 28-day Study [46]
- OECD Test Guideline 410: Repeated Dose Dermal Toxicity: 28-day Study [47]
- OECD Test Guidelines 407: Repeated Dose 28-day Oral Toxicity Study in Rodents [48]

- OECD Test Guideline 422, Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test [31]
- OPPTS Harmonized Guideline 870.3050: Repeated dose 28-day oral toxicity study in rodents [49]
- OPPTS Harmonized Guideline 870.3200: 28-Day dermal toxicity [50]

5.3.5 Data Interpretation

GHS Specific Target Organ Toxicity – Repeated Exposure [16].

5.4 ENVIRONMENTAL TOXICITY AND FATE

5.4.1 Criteria

If a solvent is an acute aquatic toxicant, then it must biodegrade rapidly and not be bioaccumulative (see Table 7, lines 1-3). If a solvent has low aquatic toxicity (Table 7, line 4), then its rate of biodegradation may be >28 days as long as the half-life < 180 days and BCF < 5000.

Table 7 – Environmental Toxicity and Fate

	Acute Aquatic Toxicity Value (L/E/IC50)^{1,2}	Persistence (Measured in terms of rate of biodegradation)	Bioaccumulation Potential
1	If ≤1 ppm...	...then may be acceptable if the component meets the 10-day window as measured in a ready biodegradation test ^c without degradation products of concern ^dand BCF <1000
2	If >1 ppm and ≤10 ppm...	...then the component must meet the 10-day window as measured in a ready biodegradation test without degradation products of concern ^d ...	
3	If >10 ppm and <100 ppm...	...then the component must meet the 28-day pass level as measured in a ready biodegradation test without degradation products of concern ^d ...	
4	If ≥100 ppm...	...then the component need not meet the 28-day pass level as measured in a ready biodegradation test if there are no degradation products of concern ^d and half-life < 180 days...	
<p>^a In general, there is a predictable relationship between acute aquatic toxicity and chronic aquatic toxicity for organic chemicals, i.e., chemicals that have high acute aquatic toxicity also have high chronic aquatic toxicity. [51] Since acute aquatic toxicity data are more readily available, the Safer Choice Criteria use these data to screen chemicals that may be toxic to aquatic life. Where measured chronic toxicity data is available, it will be assessed with other data and applied in the screen based on the relationship between acute and chronic aquatic toxicity.</p> <p>^b Data, whether estimated or measured, are required for each of the following groups of organisms algae, aquatic invertebrates and fish (all fresh water). Data for marine species may be added when available.</p> <p>^c A case-by-case approach focusing on rate of biodegradation and degradation products of concern will be implemented for solvents toxic to aquatic organisms at ≤ 1ppm.</p> <p>^d Degradation products of concern are compounds with high acute aquatic toxicity (L/E/IC50 ≤ 10ppm) which mineralize <60% in 28 days.</p>			

5.4.2 Preferred Test Methods, Persistence (measured as biodegradation)

- OECD Test Guideline 301: Ready Biodegradability (sections A-F [52]);
- OPPTS Harmonized Guideline 835.3110: Ready biodegradability [53]; and
- Modeled data from sources such as EPISuite [54] and the PBT Profiler [55] are acceptable when data are unavailable.

5.4.3 Preferred Test Methods, Bioaccumulation

A field-measured BAF (located in the literature) is the most preferred data for indicating bioaccumulation. When not possible, the following test methods may be used:

- OECD Test Guideline 305: Bioconcentration: Flow-through Fish Test [56];
- OPPTS Harmonized Guideline 850.1710: Oyster BCF [57];
- OPPTS Harmonized Guideline 850.1730: Fish BCF [58];
- Modeled data from sources such as EPISuite [54] and the PBT Profiler [55] are acceptable when data are unavailable. An estimated BAF is preferred to an estimated BCF for compounds where $\log K_{ow} > 5$.

5.4.4 Preferred Test Methods, Acute Aquatic Toxicity

A baseline data set is required that should include freshwater test data for at least one species each of algae, aquatic invertebrate and fish. Additional aquatic toxicity data in other species or in marine species will also be reviewed if available.

5.4.4.1 Preferred test methods for fish

- OECD Test Guideline 203: Fish, Acute Toxicity Test [59] and
- OPPTS Harmonized Guideline 850.1075: Fish acute toxicity test, freshwater and marine [60].

5.4.4.2 Preferred test methods for aquatic invertebrates

- OECD Test Guideline 202, Part 1, Daphnia sp., Acute Immobilisation Test [61];
- OPPTS Harmonized Guideline 850.1010: Aquatic invertebrate acute toxicity test, freshwater daphnids [62]; and
- OPPTS Harmonized Guideline 850.1035: Mysid acute toxicity test [63].

NOTE: A 96 hour Mysid shrimp acute toxicity test [70] can be used in place of a daphnid acute toxicity test when the latter is not available.

5.4.4.3 Preferred test methods for aquatic plants

- OECD Test Guideline 201, Alga, Growth Inhibition Test [64] and
- OPPTS Harmonized Guideline 850.5400: Algal toxicity, Tiers I and II [65].

5.4.5 Alternative Test Methods, Acute Aquatic Toxicity

The following test methods may be considered, when relevant:

- OPPTS Harmonized Guideline 850.1085: Fish acute toxicity mitigated by humic acid [66];
- OPPTS Harmonized Guideline 850.1025: Oyster acute toxicity test (shell deposition) [67];
- OPPTS Harmonized Guideline 850.1045: Penaeid acute toxicity test [68];
- OPPTS Harmonized Guideline 850.1055: Bivalve acute toxicity test (embryo larval) [69];
- OPPTS Harmonized Guideline 850.4400: Aquatic plant toxicity test using *Lemna spp.* Tiers I and II [70]; and
- Modeled data from sources such as ECOSAR [71] are acceptable when data are unavailable.

6 References

1. GHS, *Acute Toxicity*. 2007, United Nations.
2. USEPA. *Determining the Adequacy of Existing Data*. 1999 [cited; Available from: <http://www.epa.gov/HPV/pubs/general/datadfin.htm>].
3. USEPA. *OncoLogic™*. 2008 [cited; Available from: <http://www.epa.gov/oppt/newchems/tools/oncologic.htm>].
4. GHS, *Carcinogenicity*. 2007, United Nations.
5. OECD, *OECD Guidelines for the Testing of Chemicals: Test No. 451: Carcinogenicity Studies*. 1981.
6. OECD, *OECD Guidelines for the Testing of Chemicals: Test No. 453: Combined Chronic Toxicity/Carcinogenicity Studies*. 1981.
7. USEPA, *Health Effects Test Guidelines: OPPTS 870.4200: Carcinogenicity*. 1998.
8. USEPA, *Health Effects Test Guidelines: OPPTS 870.4300: Combined Chronic Toxicity/Carcinogenicity*. 1998.
9. NTP, *Specifications for the conduct of studies to evaluate the toxic and carcinogenic potential of chemical, biological and physical agents in laboratory animals for the National Toxicology Program*. 2006.
10. USEPA, *Guidelines for Carcinogen Risk Assessment*. USEPA Risk Assessment Forum, 2005.
11. OECD, *OECD Guidelines for the Testing of Chemicals: Test No. 424: Neurotoxicity Study in Rodents*. 1997.
12. USEPA, *Health Effects Test Guidelines: OPPTS 870.6200: Neurotoxicity Screening Battery*. 1998.
13. OECD, *OECD Guidelines for the Testing of Chemicals: Test No. 426: Developmental Neurotoxicity Study*. 2007.
14. USEPA, *Health Effects Test Guidelines: OPPTS 870.6300: Developmental Neurotoxicity Study*. 1998.
15. USEPA, *Guidelines for Neurotoxicity Risk Assessment*. Federal Register, 1998. **63**(93): p. 26926-26954.
16. GHS, *Specific Target Organ Systemic Toxicity Repeated Exposure*. 2007, United Nations.
17. USEPA, *Health Effects Test Guidelines: OPPTS 870.1100: Acute Oral Toxicity*. 1998.
18. USEPA, *Health Effects Test Guidelines: OPPTS 870.1200: Acute Dermal Toxicity*. 1998.
19. USEPA, *Health Effects Test Guidelines: OPPTS 870.1300: Acute Inhalation Toxicity*. 1998.
20. OECD, *OECD Guidelines for the Testing of Chemicals: Test No. 420: Acute Oral Toxicity - Fixed Dose Procedure*. 2001.
21. OECD, *OECD Guidelines for the Testing of Chemicals: Test No. 423: Acute Oral toxicity - Acute Toxic Class Method*. 2001.
22. OECD, *OECD Guidelines for the Testing of Chemicals: Test No. 425: Acute Oral Toxicity: Up-and-Down Procedure*. 2006.
23. OECD, *OECD Guidelines for the Testing of Chemicals: Test No. 402: Acute Dermal Toxicity*. 1987.
24. OECD, *OECD Guidelines for the Testing of Chemicals: Test No. 403: Acute Inhalation Toxicity*. 1981.
25. GHS, *Reproductive Toxicity*. 2007, United Nations.
26. OECD, *Manual for the Investigation of HPV Chemicals, Annex 1 Guidance for completing a SIDS Dossier* 2007.
27. OECD, *OECD Guidelines for the Testing of Chemicals: Test No. 415: One-Generation Reproduction Toxicity Study*. 1983.
28. OECD, *OECD Guidelines for the Testing of Chemicals: Test No. 416: Two-Generation Reproduction Toxicity*. 2001.
29. USEPA, *Health Effects Test Guidelines: OPPTS 870.3800: Reproduction and Fertility Effects*. 1998.

30. OECD, *OECD Guidelines for the Testing of Chemicals: Test No. 421: Reproduction/Developmental Toxicity Screening Test*. 1995.
31. OECD, *OECD Guidelines for the Testing of Chemicals: Test No. 422: Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test*. 1996.
32. USEPA, *Health Effects Test Guidelines: OPPTS 870.3550: Reproduction/Developmental Toxicity Screening Test*. 2000.
33. USEPA, *Health Effects Test Guidelines: OPPTS 870.3650: Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test*. 2000.
34. OECD, *OECD Guidelines for the Testing of Chemicals: Test No. 414: Prenatal Development Toxicity Study*. 2001.
35. USEPA, *Health Effects Test Guidelines: OPPTS 870.3700: Prenatal Developmental Toxicity Study*. 1998.
36. USEPA, *Guidelines for Reproductive Toxicity Risk Assessment*. Federal Register, 1996. **61**(212): p. 56274-56322.
37. USEPA, *Guidelines for Developmental Toxicity Risk Assessment*. Federal Register, 1991. **56**(234): p. 63798-63826.
38. OECD, *OECD Guidelines for the Testing of Chemicals: Test No. 408: Repeated Dose 90-Day Oral Toxicity Study in Rodents*. 1998.
39. OECD, *OECD Guidelines for the Testing of Chemicals: Test No. 409: Repeated Dose 90-Day Oral Toxicity Study in Non-Rodents*. 1998.
40. OECD, *OECD Guidelines for the Testing of Chemicals: Test No. 411: Subchronic Dermal Toxicity: 90-day Study*. 1981.
41. OECD, *OECD Guidelines for the Testing of Chemicals: Test No. 413: Subchronic Inhalation Toxicity: 90-day Study*. 1981.
42. USEPA, *Health Effects Test Guidelines: OPPTS 870.3100: 90-Day Oral Toxicity in Rodents*. 1998.
43. USEPA, *Health Effects Test Guidelines: OPPTS 870.3150: 90-Day Oral Toxicity in Nonrodents*. 1998.
44. USEPA, *Health Effects Test Guidelines: OPPTS 870.3250: 90-Day Dermal Toxicity*. 1998.
45. USEPA, *Health Effects Test Guidelines: OPPTS 870.3465: 90-Day Inhalation Toxicity*. 1998.
46. OECD, *OECD Guidelines for the Testing of Chemicals: Test No. 412: Repeated Dose Inhalation Toxicity: 28-day or 14-day Study*. 1981.
47. OECD, *OECD Guidelines for the Testing of Chemicals: Test No. 410: Repeated Dose Dermal Toxicity: 21/28-day Study*. 1981.
48. OECD, *OECD Guidelines for the Testing of Chemicals: Test No. 407: Repeated Dose 28-day Oral Toxicity Study in Rodents*. 1995.
49. USEPA, *Health Effects Test Guidelines: OPPTS 870.3050: Repeated Dose 28-day Oral Toxicity Study in Rodents*. . 2000.
50. USEPA, *Health Effects Test Guidelines: OPPTS 870.3200: 28-Day Dermal Toxicity*. 1998.
51. Rand, G.M., ed. *Fundamentals of Aquatic Toxicology*. 2nd ed. 1995, Taylor & Francis: Washington, DC.
52. OECD, *OECD Guidelines for the Testing of Chemicals: Test No. 301: Ready Biodegradability*. 1992.
53. USEPA, *Health Effects Test Guidelines: OPPTS 835.3110: Ready Biodegradability*. 1998.
54. USEPA. *EPI Suite™*. 2008 [cited June 2008]; Available from: <http://epa.gov/opptintr/exposure/pubs/episuite.htm>.
55. SRC. *PBT Profiler*. 2006 [cited June 2008]; Available from: <http://www.pbtprofiler.net/>.
56. OECD, *OECD Guidelines for the Testing of Chemicals: Test No. 305: Bioconcentration: Flow-through Fish Test*. 1996.
57. USEPA, *Health Effects Test Guidelines: OPPTS 850.1710: Oyster BCF*. . 1996.
58. USEPA, *Health Effects Test Guidelines: OPPTS 850.1730: Fish BCF*. . 1996.

59. OECD, *OECD Guidelines for the Testing of Chemicals: Test No. 203: Fish, Acute Toxicity Test*. 1992.
60. USEPA, *Health Effects Test Guidelines: OPPTS 850.1075: Fish acute toxicity test, freshwater and marine* . . 1996.
61. OECD, *OECD Guidelines for the Testing of Chemicals: Test No. 202: Daphnia sp. Acute Immobilisation Test*. 2004.
62. USEPA, *Health Effects Test Guidelines: OPPTS 850.1010: Aquatic Invertebrate Acute Toxicity Test, freshwater daphnids* . . 1996.
63. USEPA, *Health Effects Test Guidelines: OPPTS 850.1035: Mysid acute toxicity test* . . 1996.
64. OECD, *OECD Guidelines for the Testing of Chemicals: Test No. 201: Alga, Growth Inhibition Test*. 2006.
65. USEPA, *Health Effects Test Guidelines: OPPTS 850.5400: Algal toxicity, Tiers I and II* . . 1996.
66. USEPA, *Health Effects Test Guidelines: OPPTS 850.1085: Fish Acute Toxicity Mitigated by Humic Acid* . . 1996.
67. USEPA, *Health Effects Test Guidelines: OPPTS 850.1025: Oyster acute toxicity test (shell deposition)* . . 1996.
68. USEPA, *Health Effects Test Guidelines: OPPTS 850.1045: Penaeid acute toxicity test* . . 1996.
69. USEPA, *Health Effects Test Guidelines: OPPTS 850.1055: Bivalve Acute Toxicity Test (embryo larval)* . . 1996.
70. USEPA, *Health Effects Test Guidelines: OPPTS 850.4400: Aquatic plant toxicity test using Lemna spp. Tiers I and II* . . 1996.
71. USEPA. ECOSAR. 2000 [cited; Available from: <http://www.epa.gov/oppt/newchems/tools/21ecosar.htm>].