August 6, 2008

DfE SCREEN FOR SOLVENTS IN CLEANING PRODUCTS

I. OVERVIEW

To identify safer solvents for use in cleaning products, DfE focuses on the characteristics (hazard endpoints) that are relevant to the types of solvents used in cleaners and that distinguish safer solvents from those of greater concern. With cleaning 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 in the Phase I Solvents[1] (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."

DfE 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, DfE will seek data on all Attributes of Concern; data on any single attribute that does not meet DfE's 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: DfE Screen 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**

[1] Phase II solvents will include additional solvent classes used in cleaning products, such as terpenes, amines, and amides.

II. SOLVENT CLASS DEFINITIONS

A. Alcohols

Definition: An organic compound containing at least one hydroxy group (OH). Compounds having two hydroxy 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.

B. Esters

Definition: 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.

C. Ethylene glycol ethers (EGEs)

Definition: Monoethers of mono- and di-ethylene glycol, and their corresponding acetate esters; glyme and diglyme.

R-(OCH2CH2)nOH, and acetate esters
Me-(OCH2CH2)nOMe
Where R = branched or linear C1-C7 alkyl.

D. Propylene glycol ethers (PGEs)

Definition: 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_2)nOMe
Where R = branched or linear C1-C7 alkyl.

III. PREFERENCES AND TERMS

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

A. Every solvent must be screened individually. It is not expected that all solvents from these four classes will pass the screen.

B. Test data using dermal and inhalation exposure routes are preferred over oral exposure data because the former are more likely routes of exposure for cleaning products.

C. The GHS criteria and data evaluation approach, and EPA risk assessment guidance will inform professional judgment in the review of both NOAEL and LOAEL values.

D. The following terms apply in all cases [1]:

i. Dust: solid particles of a material suspended in a gas, usually air.

ii. Mist: liquid droplets of a substance or mixture suspended in a gas, usually air.
iii. Vapor: the gaseous form of a substance or mixture released from its liquid or solid state.

E. Use of existing data should follow the EPA HPV Challenge Program's data adequacy guidelines [2].

IV. 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. (see Figure 1 below).

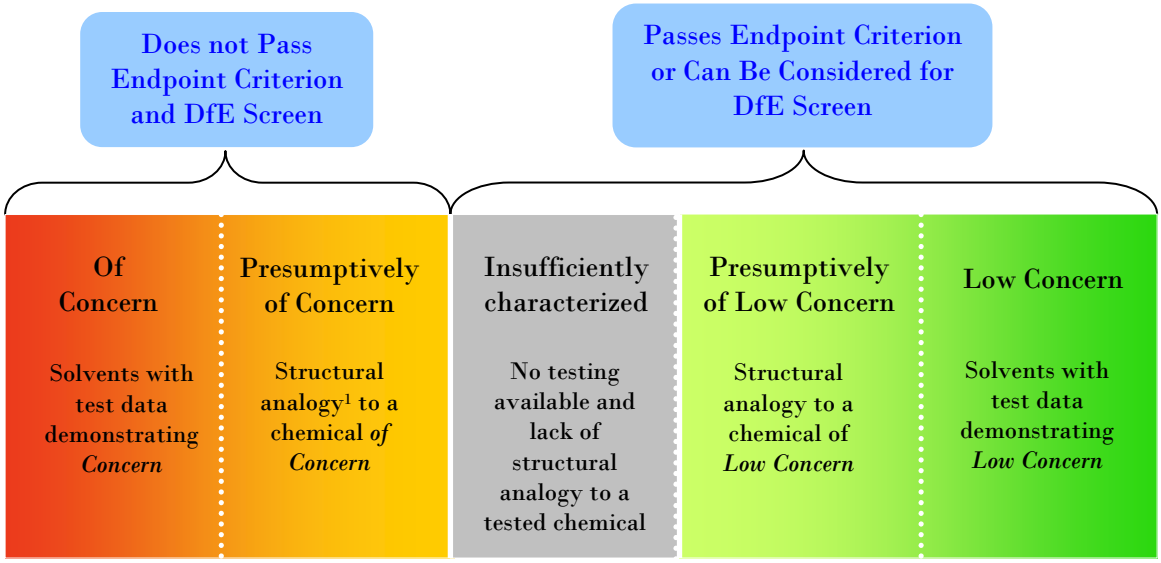

Figure 1.
A diagrammatic representation of the continuum from high concern to low concern and data requirements for screening qualification for carcinogenicity and neurotoxicity.
[1]Can also include metabolic or mechanistic analogy.

A. Carcinogenicity

i. Criteria: Phase I Solvents will be screened for carcinogenicity based upon established lists and GHS criteria, see Table 2.
ii. 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

No solvents that are classifiable as follows will pass the screen…	**According to…**
Group 1 – carcinogenic to humans Group 2A – probably carcinogenic to humans Group 2B – possibly carcinogenic to humans	International Agency for Research on Cancer (IARC)
Known to Be Human Carcinogen Reasonably Anticipated to Be Human Carcinogen	National Toxicology Program (NTP)
(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"	U.S. Environmental Protection Agency (EPA)
*Category 1 – Known or presumed human carcinogens *Category 2 – Suspected human carcinogens	Globally Harmonized System (GHS) [4]
**For chemicals where available carcinogenicity data have not been reviewed by IARC, NTP, or EPA*	

iii. Preferred study methods:
   a) OECD Test Guideline 451: Carcinogenicity Studies [5],
   b) OECD Test Guideline 453: Combined Chronic Toxicity/Carcinogenicity Studies [6].
   c) OPPTS Harmonized Guideline 870.4200 Carcinogenicity [7],
   d) OPPTS Harmonized Guideline 870.4300 Combined chronic toxicity/carcinogenicity [8].

iv. Data interpretation guidelines:
   a) See Section 2, Hazard Assessment in *Guidelines for Carcinogen Risk Assessment* [9].

B. Neurotoxicity

i. Criteria: No solvents that are classifiable as neurotoxicants according to GHS [10] (see guidance values in Table 3) will pass the screen for this endpoint. Insufficiently characterized solvents may be considered for the DfE Screen.

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

iii. Route of exposure: Data for all available routes of exposure will be evaluated. Failing to pass this endpoint by any route of exposure results in failure to pass the screen.

iv. Preferred study methods:
   a) OECD Test Guideline 424: Neurotoxicity Study in Rodents [11] and
   b) OPPTS Harmonized Guideline 870.6200 Neurotoxicity screening battery [12].

v. 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.

vi. Data interpretation guidelines:
   a) See Part A, Section 3, Hazard Characterization in *Guidelines for Neurotoxicity Risk Assessmen*t [15].

V. DISTINGUISHING ATTRIBUTES OF CONCERN

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

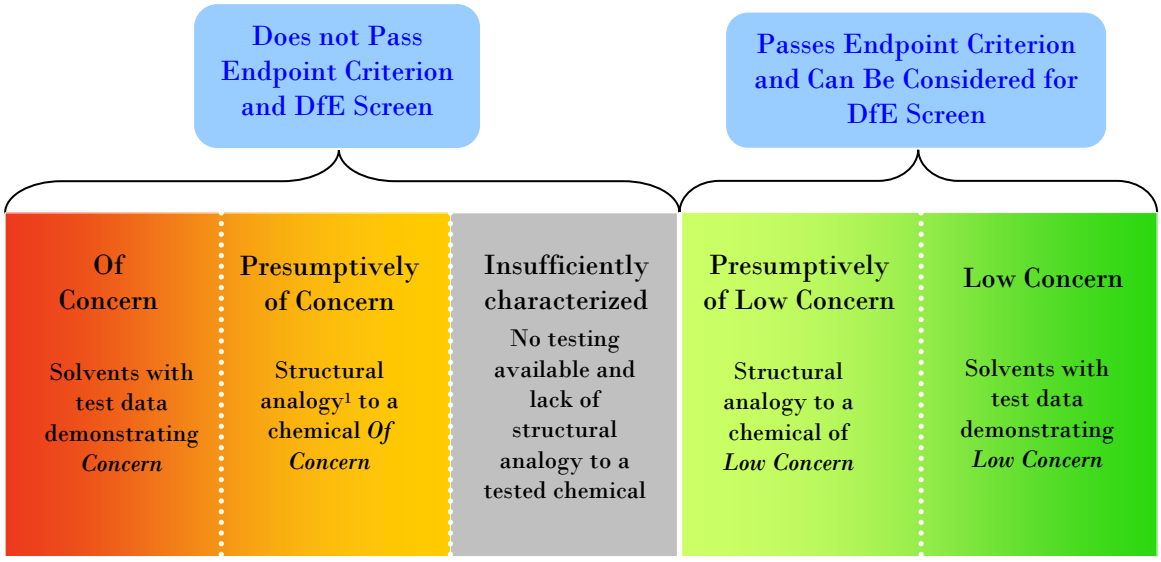

Figure 2.
A diagrammatic representation of the continuum from high concern to low concern and data requirements for screening qualification for acute toxicity, PBT, reproductive and developmental toxicity and repeated dose toxicity.
[1]Can also include metabolic or mechanistic analogy.

A. Acute Mammalian Toxicity

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

ii. 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
Oral LD_{50} (mg/kg)	>2000
Dermal LD_{50} (mg/kg)	>2000
Inhalation LC_{50} (gas) (ppm)	>5000
Inhalation LC_{50} (vapor) (mg/L)	>20
Inhalation LC_{50} (dust/mist) (mg/L)	>5

iii. Test methods:

a) OPPTS Harmonized Guideline 870.1100 Acute oral toxicity [16],

b) OPPTS Harmonized Guideline 870.1200 Acute dermal toxicity [17],

c) OPPTS Harmonized Guideline 870.1300 Acute inhalation toxicity [18].
d) OECD Test Guideline 420: Acute Oral Toxicity-Fixed Dose Method [19],
e) OECD Test Guideline 423 Acute Oral Toxicity – Acute Toxic Class Method [20],
f) OECD Test Guideline 425 Acute Oral Toxicity – Up-and-Down Procedure [21],
g) OECD Test Guideline 402 – Acute Dermal Toxicity [22],
h) OECD Test Guideline 403 – Acute Inhalation Toxicity [23].

B. Reproductive and Developmental Toxicity

i. Criteria: Phase I Solvents will not be acceptable under the screen if they are classifiable as reproductive toxicants according to GHS [24] (see guidance values in Table 5). Following the SIDS Dossier [25], all solvents must be reviewed for both fertility and developmental effects.
ii. Data Evaluation: Data on reproductive and developmental toxicity must be available via at least one of the above routes of exposure. Data for all available routes of exposure will be evaluated. Failing 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

iii. Preferred test methods - Fertility:
a) OECD Test Guideline 415: One-Generation Reproduction Toxicity Study [26], or
b) OECD Test Guideline 416: Two-Generation Reproduction Toxicity Study [27].
iv. Acceptable test methods - Fertility:
a) OPPTS 870.3800 Reproduction and fertility effects [28].

b) Per GHS [24], results from OECD Test Guideline 421, Reproduction/Developmental Toxicity Screening Test [29]; OECD Test Guideline 422, Combined Repeated Dose Toxicity Study with the Reproduction/ Developmental Toxicity Screening Test [30]; OPPTS Harmonized Guideline 870.3550 Reproduction/ developmental toxicity screening test [31]; or 870.3650 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test [32] can also be used to justify classification.

v. Preferred test methods – Developmental Toxicity:
   a) OECD Test Guideline 414: Prenatal Developmental Toxicity Study [33].

vi. Acceptable test methods – Developmental Toxicity:
   a) OPPTS 870.3700 Prenatal developmental toxicity study [34].
   b) Per GHS [24], results from OECD Test Guideline 421, Reproduction/Developmental Toxicity Screening Test [29]; OECD Test Guideline 422, Combined Repeated Dose Toxicity Study with the Reproduction/ Developmental Toxicity Screening Test [30]; OPPTS Harmonized Guideline 870.3550 Reproduction/ developmental toxicity screening test [31]; or 870.3650 Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test [32] can also be used to justify classification.

vii. Data interpretation guidelines:
   a) See, See Part A, Section 3, Hazard Characterization in *Guidelines for Reproductive Toxicity Risk Assessmen*t [35] and
   b) *Guidelines for Developmental Toxicity Risk Assessment* [36].

C. Repeated Dose Toxicity

i. Criteria: Phase I Solvents will not be acceptable under the screen if they are classifiable as systemic toxicants according to GHS [10] (see guidance values in Table 6).

Table 6: Repeated Dose Toxicity

Route of Exposure	Guidance values*
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
**The 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.*	

ii. 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. Failing to pass this screen by any route of exposure results in failure of this endpoint under the screen. 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.

iii. Preferred test methods:
   a) OECD Test Guideline 408: Repeated Dose 90-Day Oral Toxicity Study in Rodents [37],
   b) OECD Test Guideline 409: Repeated Dose 90-Day Oral Toxicity Study in Non-Rodents [38],
   c) OECD Test Guideline 411: Subchronic Dermal Toxicity: 90-day Study [39],
   d) OECD Test Guideline 413: Subchronic Inhalation Toxicity: 90-day Study [40].
   e) OPPTS Harmonized Guideline 870.3100 90-Day oral toxicity in rodents [41],
   f) OPPTS Harmonized Guideline 870.3150 90-Day oral toxicity in nonrodents [42],
   g) OPPTS Harmonized Guideline 870.3250 90-Day dermal toxicity [43],
   h) OPPTS Harmonized Guideline 870.3465 90-Day inhalation toxicity [44].

iv. Acceptable test methods:
   a) OECD Test Guideline 412: Repeated Dose Inhalation Toxicity: 28-day [45],
   b) OECD Test Guideline 410: Repeated Dose Dermal Toxicity: 28-day Study [46],
   c) OECD Test Guidelines 407: Repeated Dose 28-day Oral Toxicity Study in Rodents [47],
   d) OECD Test Guideline 422, Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test [30],
   e) OPPTS Harmonized Guideline 870.3050 Repeated dose 28-day oral toxicity study in rodents [48],
   f) OPPTS Harmonized Guideline 870.3200 28-Day dermal toxicity [49].

v. Data interpretation guidelines: Specific Target Organ Systemic Toxicity Repeated Exposure [10].

D. Environmental Toxicity and Fate

i. Criteria: If a solvent is an acute aquatic toxicant, then it must biodegrade rapidly and not be bioaccumulative (see Table 7, 1-3). If a solvent has low aquatic toxicity (Table 7, 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 biodegradation[3] occurs within a 10-day window[4]…	**…and** BCF <1000
2	**If** >1 ppm and ≤10 ppm…	**…then** biodegradation[3] must occur within a 10-day window…	
3	**If** >10 ppm and <100 ppm…	**…then** biodegradation[3] must occur within 28 days without products of concern[5]…	
4	**If** ≥100 ppm…	**…then** biodegradation[3] need not occur within 28 days if there are no products of concern[5] and half-life <180 days…	**…and** BCF <5000

[1] 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. [50] Since acute aquatic toxicity data are more readily available, the DfE Screens use these data to screen chemicals that may be toxic to aquatic life.

[2] At least one test for each of the following groups of organisms is required: algae, aquatic invertebrates and fish (all fresh water). Data for marine species may be added when relevant.

[3] Generally, >60% mineralization (to CO_2 and water).

[4] 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.

[5] Products of concern are compounds with high acute aquatic toxicity (L/E/IC50 ≤ 10ppm) and a slow rate of biodegradation (greater than 28 days).

ii. Persistence (measured as biodegradation) Test Guidelines

a) Preferred Test Methods
   1) OECD Test Guideline 301: Ready Biodegradability (sections A-F [52]).
   2) OPPTS Harmonized Guideline 835.3110 Ready biodegradability [51].

b) Modeled data from sources such as EPISuite [53] and the PBT Profiler [54] are acceptable when data are unavailable.

iii. Preferred Methods for Bioaccumulation

a) A field-measured BAF (located in the literature) is the most preferred data for indicating bioaccumulation.

b) When not possible, the following test methods may be used:
    1) OECD Test Guideline 305: Bioconcentration: Flow-through Fish Test [55].
    2) OPPTS Harmonized Guideline 850.1710 Oyster BCF [56],
    3) OPPTS Harmonized Guideline 850.1730 Fish BCF [57].
    4) Modeled data from sources such as EPISuite and the PBT Profiler are acceptable when data are unavailable. An upcoming version of EPISuite will estimate bioaccumulation factor and this will be preferred to estimated BCF.

iv. Acute Aquatic Toxicity Guidelines

a) 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.
b) Preferred Test Methods for Fish
    1) OECD Test Guideline 203: Fish, Acute Toxicity Test [58],
    2) OPPTS Harmonized Guideline 850.1075 Fish acute toxicity test, freshwater and marine [59].
c) Preferred Test Methods for Aquatic Invertebrates
    1) OECD Test Guideline 202, Part 1, Daphnia sp., Acute Immobilisation Test [60],
    2) OPPTS Harmonized Guideline 850.1010 Aquatic invertebrate acute toxicity test, freshwater daphnids [61],
    3) OPPTS Harmonized Guideline 850.1035 Mysid acute toxicity test[B] [62].
d) Preferred Test Methods for Aquatic Plants
    1) OECD Test Guideline 201, Alga, Growth Inhibition Test [63].
    2) OPPTS Harmonized Guideline 850.5400 Algal toxicity, Tiers I and II [64].
e) Alternative test methods that may be considered when relevant:
    1) OPPTS Harmonized Guideline 850.1085 Fish acute toxicity mitigated by humic acid [65],
    2) OPPTS Harmonized Guideline 850.1025 Oyster acute toxicity test (shell deposition) [66],

[B] A 96 hour Mysid shrimp acute toxicity test [66] can be used in place of a daphnid acute toxicity test [64 & 65] when the latter is not available.

3) OPPTS Harmonized Guideline 850.1045 Penaeid acute toxicity test [67],
4) OPPTS Harmonized Guideline 850.1055 Bivalve acute toxicity test (embryo larval) [68],
5) OPPTS Harmonized Guideline 850.4400 Aquatic plant toxicity test using *Lemna spp.* Tiers I and II [69].

f) Modeled data from sources such as ECOSAR [70] are acceptable when data are unavailable.

VI. References

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