Comments on the Design for the Environment (DfE) Program Alternatives Assessment for the Flame Retardant Decabromodiphenyl ether

Non-508 Compliant Attachments

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BASF

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Decabromodiphenyl Ether Flame Retardant in Plastic Pallets

A Safer Alternatives Assessment

Appendices

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Appendix 1

Distributors of Plastic Pallets

Company Name	Address
Name	Location
Akro-Mils	Akron, Ohio United States
Albion Industries	Albion, Michigan United States
B & R Unifuse	Staatsburg, New York United States
Cadillac Industrial Products Co.	Troy, Michigan United States
Cartonplast LLC	De Forest, Wisconsin United States
Casemaker Inc.	Thornhill, ON Canada
Colson Caster Corp.	Jonesboro, Arkansas United States
Convoy, Inc.	Canton, Ohio United States
Cookson Plastic Molding	Latham, New York United States
Creative Techniques, Inc.	Auburn Hills, Michigan United States
DIC Intl. USA Inc.	Ft. Lee, New Jersey United States
Dynaric, Inc.	Virginia Beach, Virginia United States
EAM Mosca Corp.	West Hazleton, Pennsylvania United States
Faultless Caster	Evansville, Indiana United States
FKI Logistex Automation Div.	Cincinnati, Ohio United States
Flexcon Container	Springfield, New Jersey United States
Frost Inc.	Grand Rapids, Michigan United States
General Container Corp.	Somerset, New Jersey United States

Globe Composite Solutions	Rockland, Massachusetts United States
Goodwrappers	Baltimore, Maryland United States
Gould Plastics, Inc.	Duluth, Georgia United States
Hoover Materials Handling Group, Inc.	Alpharetta, Georgia United States
Intech Corp.	Closter, New Jersey United States
Interroll Corp.	Wilmington, North Carolina United States
IPL Products, Ltd.	Worcester, Massachusetts United States
Jarvis Caster Group	Palmer, Massachusetts United States
JECO Plastic Products, LLC	Plainfield, Indiana United States
Kornylak Corp.	Hamilton, Ohio United States
Linpac Materials Handling	Georgetown, Kentucky United States
LINPAC Materials Handling	Georgetown, Kentucky USA
Lyon Workspace Products	Aurora, Illinois United States
Macro Plastics, Inc.	Fairfield, California United States
Melmat Inc.	Huntington Bch., California United States
Mid-States Engrg. & Mfg., Inc.	Milton, Iowa United States
Molded Fiber Glass Tray Co.	Linesville, Pennsylvania United States
Molded Materials Inc.	Plymouth, Michigan United States
Ohio Rack, Inc.	Alliance, Ohio United States
OptiLogistics, Inc.	Irving, Texas United States
Pacific Bin Corp.	Bellevue, Washington United States
PDQ Plastics, Inc.	Bayonne, New Jersey United States
Plastic Products, Inc.	Schaumburg, Illinois United States
Port Erie Plastics	Harborcreek, Pennsylvania United

	States
Protecta-Pack Systems	Minneapolis, Minnesota United States
Quantum Storage Systems	Opa-Locka, Florida United States
Rampmaster Inc.	Miami, Florida United States
Regplas, Inc.	Mission, Kansas United States
Remcon Plastics, Inc.	Reading, Pennsylvania United States
SCA Packaging North America	New Brighton, Pennsylvania United States
Sealed Air Corp.	Danbury, Connecticut United States
Sealed Air Corp.	Saddle Brook, New Jersey United States
SFB Plastics, Inc.	Wichita, Kansas United States
Shuert Industries Inc.	Sterling Hts., Michigan United States
Signode Packaging Systems	Glenview, Illinois United States
SJF Material Handling Inc.	Winsted, Minnesota United States
SKF USA	Bethlehem, Pennsylvania United States
Smith Companies, Inc.	Pelham, Alabama United States
Sol Plastics. L.P.	Montreal, QC Canada
Superior Tire & Rubber Co.	Warren, Pennsylvania United States
Tente Casters, Inc.	Hebron, Kentucky United States
Timco Inc.	Peekskill, New York United States
Tote Systems Inc.	Burleson, Texas United States
Transpac Corp.	Lansing, Michigan United States
UFP Technologies Inc.	Georgetown, Massachusetts United States
Vestil Mfg. Co.	Angola, Indiana United States

Appendix II

Grocery Industry Pallet Performance Specifications[1]

1) Exact 48-inch x 40-inch dimensions. Square in each direction.

2) True four-way entry. Capable of accommodating existing pallet jacks from all four sides (as opposed to current style with cutouts and stringers).

3) Minimum-width pallet jack openings of 12 inches and minimum height of **3-** 3/4 inch clearance when under load. Width of each center support must be less than six inches to accommodate pallet jacks.

4) Smooth, non-skid, top-bearing surface should have at least 85% coverage. However, 100% is preferred. Non-skid surface should be flat, or have no indentations or protrusions that could cause product damage.

5) Bottom-bearing surface of no less than 60% coverage with properly placed cut-outs (12-inches square) for pallet jack wheels from four sides. Surface should be flat or have no indentations or protrusions that could cause product damage.

6) All bottom entry edges should be chamfered to 114-inch for easy entry and exit.

7) Overall height of platform should not exceed six inches.

8) Rackable from both the 48-inch and 40-inch dimensions. Allowable deflection in drive-in and drive-through racks no more than 112 inch.

9) Compatible with pallet conveyors, pallet dispensers, skate-wheel pallet-flow racks, and automatic storage and retrieval systems.

10) No protruding fasteners.

[1] Grocery Manufacturers of America, Grocery Industry Pallet SubCommittee (written by Cleveland Associates), "Recommendations on the Grocery Industry Pallet System," p.11.

11) Must be made of material that does not contaminate the product it carries.

12) Must meet or exceed current pallet resistance to fire.

13) Must be recyclable. Preferably made from recycled material.

14) Desired weight under 50 pounds.

15) Load capacities of 2,800 pounds. Capable of bearing 2,800-pound loads safely in stacks five loads high.

16) Repairs should be economically feasible.

17) Weather resistant.

18) Moisture resistant.

19) Capable of safely moving product, damage free, through the entire distribution channel with multiple cycles (from manufacturer through distributor to retail).

Appendix III

Idle Material Handling Products (FM Approval Class Number 4996)

The storage of idle material handling products in warehouses or manufacturing facilities can represent a severe challenge to automatic sprinkler protection systems. Products such as pallets, tote boxes, bins or protective cases, especially when manufactured from plastic, wood or cellulosic materials, normally require a very high sprinkler water discharge rate for adequate protection.

While doing extensive research testing, FM Approvals has developed a system and a test methodology to determine if the tested material can be protected as equivalent to wood pallets.

All FM Approved material handling products have been tested according to FM Approvals Standard 4996, "The Classification of Idle Plastic Pallets as Equivalent to Wood Pallets." The Approvals standard specifically addresses idle plastic pallets.

For specific sprinkler protection recommendations, refer to FM Global Property Loss Prevention Data Sheet 8-9, "Storage of Class 1, 2, 3, 4 and Plastic Commodities" and FM Global Property Loss Prevention Data Sheet 8-24, "Idle Pallet Storage."

Approval recognition is extended only to those products which exhibit burning and heat release characteristics equivalent to or less critical than conventional wood pallets. Each FM Approved product shall bear an Approval mark.

...

Plastic Pallets (Class Number 4996)

Group Products by Company

CHEP International Inc
8517 South Park Circle, Orlando, Florida 32819, USA

Product	Listing Country	Certification Type
P4840B	United States of America	FM Approved
B4840A	United States of	FM

Product	Listing Country	Certification Type
	America	Approved

iGPS Company LLC
225 East Robinson St, Suite 200, Orlando, Florida 32801, USA

Product	Listing Country	Certification Type
BiPP4840 HR 6R iGPS Pool Pallet	United States of America	FM Approved

Orbis Corporation
1055 Corporate Center Dr, Oconomowoc, Wisconsin 53066-0389, USA

Product	Listing Country	Certification Type
Model 1200x1000 (39x47) FM SuperPal	United States of America	FM Approved
Model 36 × 42 FM FG	United States of America	FM Approved
Model 36 × 48 FM FG	United States of America	FM Approved
Model 40 × 48 FM BulkPal	United States of America	FM Approved
Model 40 × 48 FM HDSC	United States of America	FM Approved
Model 40 × 48 FM RACK'R	United States of America	FM Approved
Model 40 × 48 FM RCKO	United States of	FM

Product	Listing Country	Certification Type
	America	Approved
Model 40 × 48 FM RCKO LP	United States of America	FM Approved
Model 40 × 48 OP FM CIISF	United States of America	FM Approved
Model 40 × 48 OP FM CIISF LP	United States of America	FM Approved
Model 40x48 Stack'R Pallet	United States of America	FM Approved
Model 42 × 48 FM HDSC	United States of America	FM Approved
Model 44 x 56 DC HI	United States of America	FM Approved
Model 44 x 56 DC LO	United States of America	FM Approved
Model 44 x 56 OCP	United States of America	FM Approved
Model 45 × 48 FM HD Lip A	United States of America	FM Approved
Model 45 × 48 FM HD Lip B	United States of America	FM Approved
Model 45 × 48 FM HD Lip C	United States of America	FM Approved
Model 45 × 48 FM JOURNEY	United States of America	FM Approved
Model 48 × 48 FM Drum OP CIISF	United States of America	FM Approved

Product	Listing Country	Certification Type
Model 48 × 48 FM HD DRM	United States of America	FM Approved
Model 48 × 48 FM HDSC	United States of America	FM Approved
Models 40 × 48 FM GrabPal 2.5",3.7," GrabPal 3.0" con	United States of America	FM Approved

Plastics Research Corporation
1400 South Campus Ave, Ontario, California 91761-4330, USA

P/N 105250-101 is a high performance composite pallet designed to comply with GMA requirements for a 40 x 48 in (1 x 1.2 m), 4-way, rackable, non-reinforced pallet, capable of multi-trip duty. This pallet does not contain decca-bromine.

Product	Listing Country	Certification Type
P/N 105250-101 Plastic Pallet	United States of America	FM Approved

Polymer Solutions International
15 Newtown Wood Road, Newtown Square, Pennsylvania 08055, USA

Product	Listing Country	Certification Type
4048 Prostack general purpose plastic pallets	United States of America	FM Approved
4048 Prostack with Lip general purpose plastic pallets	United States of America	FM Approved
4048 Prostack with Cleat and Corner Openings plastic pallets	United States of America	FM Approved

Schoeller Arca Systems Inc
3000 Town Center, Suite 620, Southfield, Michigan 48075, USA

Product	Listing Country	Certification Type
BiPP4840 HR 6R iGPS	United States of America	FM Approved

TMF Corporation
850 West Chester Pike, Suite #303, Havertown, Pennsylvania 19083-4439, USA

Product	Listing Country	Certification Type
Model Protech 4048	United States of America	FM Approved

Appendix IV: UL 2335 Classified Pallets

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Guide Information	Pallets, Storage	*QENL.GuideInfo*
POLYMER PALLETS L L C	Pallets, Storage	*QENL.R19299*
REHRIG PACIFIC CO	Pallets, Storage	*QENL.R20575*
SCHOELLER ARCA SYSTEMS INC	Pallets, Storage	*QENL.R25482*

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QENL.R25484

Pallets, Storage

See General Information for Pallets, Storage

CHEP EQUIPMENT POOLING SYSTEMS R25484

8517 S PARK CIR

ORLANDO, FL 32819 USA

Pallet Name	General Description	Pallet Length (inches)	Pallet Width (inches)
P4840B - V2.0	Four-Way Entry, Block Pallet	48	40

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Pallets, Storage

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POLYMER PALLETS L L C R19299

U S 422

15567 MAIN MARKET RD

PO BOX 674

PARKMAN, OH 44080 USA

Pallet Name	General Description	Pallet Length (inches)	Pallet Width (inches)
Polymer Pallet	PVC Two-Way Entry, Stringer Pallet	48	48
Polymer Pallet	PVC Two-Way Entry, Stringer Pallet	48	42
Polymer Pallet	PVC Two-Way Entry, Stringer Pallet	42	48

Polymer Pallet	PVC Two-Way Entry, Stringer Pallet	44	44
Polymer Pallet	PVC Two-Way Entry, Stringer Pallet	48	40
Polymer Pallet	PVC Two-Way Entry, Stringer Pallet	40	48
Polymer Pallet	PVC Two-Way Entry, Stringer Pallet	42	42
Polymer Pallet	PVC Two-Way Entry, Stringer Pallet	36	48
Polymer Pallet	PVC Two-Way Entry, Stringer Pallet	40	40
Polymer Pallet	PVC Two-Way Entry, Stringer Pallet	36	36
Polymer Pallet	PVC Four-Way Entry, Block Pallet	48	48
Polymer Pallet	PVC Four-Way Entry, Block Pallet	48	42
Polymer Pallet	PVC Four-Way Entry, Block Pallet	42	48
Polymer Pallet	PVC Four-Way Entry, Block Pallet	44	44
Polymer Pallet	PVC Four-Way Entry, Block Pallet	48	40
Polymer Pallet	PVC Four-Way Entry, Block Pallet	40	48
Polymer Pallet	PVC Four-Way Entry, Block Pallet	42	42
Polymer Pallet	PVC Four-Way Entry, Block Pallet	36	48
Polymer Pallet	PVC Four-Way Entry, Block Pallet	40	40
Polymer Pallet	PVC Four-Way Entry, Block Pallet	36	36

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REHRIG PACIFIC CO R20575

4010 E 26TH ST

LOS ANGELES, CA 90023 USA

Pallet Name	General Description	Pallet Length (inches)	Pallet Width (inches)
HuskyLite Snap-Lock Pallet	Four-Way Entry, Block Pallet	48	40
HuskyLite Snap-Lock Pallet	Four-Way Entry, Block Pallet	48	36
HuskyLite Snap-Lock Pallet	Four-Way Entry, Block Pallet	43	37
HuskyLite Snap-Lock	Four-Way Entry, Block	41.3	37.4

Pallet	Pallet		
HuskyLite Snap-Lock Pallet	Four-Way Entry, Block Pallet	37	37

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Pallets, Storage

Pallets, Storage

See General Information for Pallets, Storage

SCHOELLER ARCA SYSTEMS INC R25482

SUITE 110

5202 OLD ORCHARD RD

SKOKIE, IL 60077 USA

Pallet Name	General Description	Pallet Length (inches)	Pallet Width (inches)
BiPP 4840 HR 6R iGPS PoolPallet-SAS	Four-Way Entry, Block Pallet	48	40

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Appendix V

Polymer Range for Flame Retardant Plastic Pallets

Prepared for this report by:
James Innes & Ann Innes
Flame Retardants Associates

The polymer resins most likely to be chosen by a formulator for the flame retardant plastic pallet application include the polyolefins (PP, PE) and/or MPPO. The polyolefin resins are from a technical perspective the easiest to flame retard while retaining the physical properties required for a plastic pallet AND doing so at the least cost to produce.

Further, after significant review of flame retardant plastic pallet technology and marketplace, it is apparent to the authors that only two specific polyolefin polymer resins will practically fit the flame retardant plastic pallet application. These are HDPE, high density polyethylene, and polypropylene copolymer or impact modified polypropylene. The process for making the pallet is injection molding (although there are some thermoformers). The pallet making process largely governs the selection of melt flow of the chosen polymer. The polymer must be able to be injection molded in such a process; i.e., melt flow appropriate for the process. Either virgin resin or post-industrial recycle resin would be chosen. Of importance to note is that HDPE is the resin found in most post-consumer PE as it is used in the overly- abundant milk containers sold across the country. This is a blow molding grade and is not applicable to injection molding. The table below is an abbreviated list of polypropylene and HDPE suppliers, trade names and grades of HDPE that could fit the flame retardant plastic pallet application.

HDPE Suppliers, Trade Names, HDPE Grades

Suppliers	**Trade Names**	**Grades/Comments**
Chevron Phillips	Marlex HWN4550 HDPE 5 MFI*	Tensile Strength 3500^{+} psi Flex Modulus 160-180 (10^3 psi ASTM D790) Izod Impact 6^{+} fl lb/in (Notched)
Equistar Chemicals LP	Alathion M4661 HDPE 6 MFI	
Exxon Mobil	Escorene HD 6705 HDPE Escorene HD 0358 HDP	
Ineos	Fortilene KG4685 PP	
Phillips Sumika	Marlex AGN120	
Equistar Chemicals	Petrothene PP38NR01X01	
Lyondell Basell	Moplen EP340M	

*MFI = Melt Flow Index

In the 1990's GE Plastics, now SABIC, developed several new applications for their Noryl® polymer. This included a "plastic house" and they did also develop a plastic pallet which actually

went through the requisite pallet testing at FM to prove the formulation met the FM standard for idle pallets. Noryl® is modified polyphenylene oxide (or ether) blended with high impact polystyrene or HIPS. The amount of HIPS in the formulation depends on the flow needed for the application. In addition to these two polymers, the formulations also include 10-15% of a phosphate ester plasticizer which results in a UL94 V0 formulation. [A lower loading (~6-8%) of the phosphate ester would likely result in a pass in the idle pallet test; however, physical properties would require consideration.] Various plasticizers have been used since the initial development. Most recently, these have been alkylated phenol phosphate or bisphenol A diphosphate. The pallet produced was deemed to be too expensive to market and, as a result, GE did not renew the certification with FM and did no further development. Flame Retardants Associates estimates that a pallet produced with Noryl® which meets the pallet standards would be in the economically prohibitive range of over $90/pallet. Also, there is little or no post-industrial MPPO available in the recycle marketplace which could result in lower cost.

Appendix VI

The Cost Factor and Flame Retardant Plastic Pallets

Prepared for this report by:
James Innes & Ann Innes
Flame Retardants Associates

Specific gravity is an important concept to understand. Why? Because it directly impacts the cost factor for producing a pallet. Indeed, it is the controlling part of the cost factor. Specific gravity can be defined as the density (mass per unit volume) of any material divided by that of water at a standard temperature (usually 4^{o}C). Since water's density is nearly 1.00 g/cc, density in g/cc and specific gravity are nearly equal.

What does this mean? For a given volume of material, a plastic compound with a lower specific gravity will produce a part with lower weight. Or it actually takes less pounds of material to fill a mold to produce the part. A given amount of a plastic compound or formulation with a lower specific gravity will produce more parts than another formulation with a relatively higher specific gravity. Molds are filled on a volume basis, not weight. One of the resulting "tricks of the trade" is knowing that a less costly formulation which meets all the part's requirements across the board may simply not be economically attractive if its specific gravity is too high. In other words, needing more of the compound to fill the mold often wipes out the advantage of the lesser cost per pound.

From this point forward, a review of formulation costs incorporating the absolutely required specific gravity factor will be presented. This should help the reader understand how to do the cost calculation as well as the direct impact on cost of specific gravity.

If a 40" x 48" rackable standard pallet weighs 44.2 pounds using a non-flame retardant PP resin, flame retardant (FR) versions will produce pallets weighing amounts different than that. See Table App-VI-1 for the calculations which incorporate specific gravity data. These calculations assume a 0.9 specific gravity for the PP resin and a 0.95 specific gravity for the DECA/antimony trioxide FR system, and 1.048 for the MDH FR system.

Table App-VI-1. Calculating the Weight of FR Plastic Pallets

PP Pallet (no FR) Weight	Weight of Pallet with Deca/Antimony as FR	Weight of Pallet with MDH as FR
44.2 pounds	44.2/0.9 x 0.95[1] = 46.65 pounds	44.2/0.9 x 1.048 = 51.46 pounds

[1] Let's assume a 50 pound pallet which contains 3.4 pounds of DECA and 1.133 pounds of antimony trioxide (this is a 3 to 1 ratio). A formulator would probably do a calculation using an even 100 pounds. So the calculation of the 0.95 specific gravity for the DECA/antimony/PP system is obtained as follows:

90.934 pounds PP sp grav of 0.9	0.90934/0.9 = 1.0103 cc (cubic centimeters)
6.8 pounds DECA sp grav 3.25	0.068/3.25 = 0.0292 cc
2.266 pounds antimony trioxide sp grav 5.6	0.02266/5.6 = 0.0040 cc
	Total cc = 1.0435 cc
	Or for the DECA FR system 1/1.0435 = 0.095 sp gravity

The iGPS Pallet

Now, as an example, let's look at some hypothetical calculations for the iGPS FR pallet, starting with specific gravity.. This pallet is made from HDPE, not PP, and is flame retarded with a DECA/antimony trioxide system. It contains about 3.4 pounds DECA and is expected to contain 1.133 pounds antimony trioxide using a 3 to 1 ratio (which is typical for this system). Let's convert this 48.5 pound pallet to a formulation batch weighing 100 pounds to make the calculations easier.

3.4 pounds DECA/ 48.5 pounds pallet mass = 7.01% loading (let's round that to 7.0)

1.133 pounds antimony trioxide/48.5 pounds pallet mass = 2.37% loading

We have 7 pounds of DECA + 2.37 pounds of antimony trioxide = 9.37 pounds. So in a 100 lbs batch, that means we have 90.63 pounds of HDPE (or this is a 90.63% loading).

We know the specific gravity of HDPE ranges from 0.952 to 0.965, so let's use 0.96 for our calculation here.

0.9063 HDPE/0.96 sp grav = 0.9440

0.070 DECA/3.25 sp grav = 0.0215

0.0237 Sb_2O_3/5.6 sp grav = 0.0042

Total = 0.9697 cc/gram

1/0.9697 = **1.0312** specific gravity for this DECA/Antimony HDPE formulation. This is the density of this formulation in grams per cc.

Now let's move on to some cost calculations for this iGPS DECA FR HDPE pallet.

A simple calculation of total formulation raw material cost per pound using the raw material component costs would be done as shown in Table 14. In this table, the colorants/stabilizer cost/pound was gathered from current commercial stabilizer/colorant suppliers.

Table App-VI-2. Simple DECA FR HDPE formulation cost calculation

Formulation Component	Loading	Cost/pound	Component Cost
HDPE	88.63%	$0.80	$0.709
DECA	7.0%	$1.80	$0.126
Antimony Trioxide (Sb_2O_3)	2.37%	$3.00	$0.0711
Colorants/Stabilizers	2%	$2.50	$0.05
Formulation Total Cost/pound			$0.9561

But the reality of actually trying to produce a formulation like this and push it into an injection molding machine to produce a large part like a pallet means that in all likelihood a masterbatch would be used. This masterbatch (think concentrate) is let down in the pallet injection molding machine at a loading level that produces the required amount of FR system in the formulation being injected into the pallet mold. A masterbatch is produced by a masterbatch compounder. See Figure App-VI-1 for a list of known commercial suppliers of masterbatch compound. Each has supplied a full range of masterbatch needed for plastic pallet manufacture.

Masterbatch Supplier	Location
Spartech Polycom	Denora, PA
Washington Penn Plastics	Washington, PA
PolyOne Corporation	Avon Lake, OH
Phoenix Plastics	Conroe, TX
Saco Polymers (formerly Padanaplast)	Aurora, OH
Hanson Company	Duluth, GA

Figure App-VI-1. Commercial Masterbatch Suppliers

A typical masterbatch would contain 60% active FR in a HDPE. See Table App-VI-3 for the masterbatch cost calculation.

Table App-VI-3. DECA/Antimony Trioxide HDPE Masterbatch Cost Calculation

Formulation Component	Loading	Cost/pound	Component Cost
HDPE	40%	$0.80	$0.32
DECA	44.82%	$1.80	$0.806
Antimony Trioxide (Sb_2O_3)	15.18%	$3.00	$0.455
Formulation Total Cost/pound			$1.581

The cost calculation for this masterbatch plus the cost to compound plus a markup for profit gives a good estimate of the sell price per pound of this masterbatch to the pallet molder. In this case, let's assume $0.20/pound as a cost of compounding which gives a cost of $1.781/pound for the masterbatch producer to produce this formulation. The masterbatch producer will mark this up to make a profit so let's assume a 30% markup. This produces a cost per pound to the pallet injection molder of $2.54. Now let's use this cost and recalculate in Table App-VI-4 the raw material cost for the iGPS FR pallet (in other words, we are now re-doing the calculation costs in Table App-VI-2 to reflect real world use of masterbatch). To provide the required 7% DECA in 100 pounds of the final compound, 15.61 pounds of the $2.54/pound masterbatch will be required. (7% / 44.82% = 15.6%)

Table App-VI-4. Pallet Formulation Cost Calculation Using Deca FR Masterbatch

Formulation Component	Loading	Cost/pound	Component Cost
HDPE	82.39%	$0.80	$0.659
DECA Masterbatch	15.6%	$2.54	$0.396
Colorants/Stabilizers	2%	$2.50	$0.05
Formulation Total Cost/pound			$1.105

So a better estimate of the raw material cost per pound for the Deca FR pallet is $1.105 rather than the $0.9561 computed in Table App-VI-2.

More Costs – Plastic Resins and Plastic Pallets

The cost of producing a flame retardant plastic pallet varies significantly depending on the base resin and the chosen flame retardant. Table App-VI-5 shows price ranges for three of the more likely resins for the FR plastic pallet application. [Plastics News, 9/27/10, pp. 21-22]

Table App-VI-5. Price Ranges for Likely Plastic Pallet Resins

Resin	Grade/Description	Price range/pound
HDPE	Injection Molding Recycle	\$0.80-\$0.85 \$0.41-\$0.45
PP	Injection General Purpose Large Buyers* Recycle Industrial	\$0.97-\$1.03 \$0.66 - \$0.67 \$0.62-\$0.68
PPO/PPE	Injection General Purpose	\$1.23-\$1.87

*London Metals Exchange for very large buyers, Plastics News, Sept 6, 2010

Cost to purchase pallets in the pallet industry today ranges from \$5 per pallet for a wood pallet to \$60 per pallet for a 50 pound plastic (non-FR) pallet to a halogen FR pallet at about \$100 per pallet which weigh about 55 pounds.

Plastic Pallet using a Metal Hydrate FR system

Now let's look at the cost to produce a plastic pallet using PP and a MDH (magnesium hydroxide) non-halogen flame retardant. Since we now live in the real world, we need to calculate a masterbatch cost first. See Table App-VI-6.

Table App-VI-6. Cost Calculation for non-halogen FR Masterbatch

Formulation Component	Loading	Cost/pound	Component Cost
PP	28%	\$1.00	\$0.28
MDH	70%	\$0.35	\$0.245
Processing Aid	2%	\$1.20	\$0.024
Formulation Total Cost/pound			\$0.549

Adding a $0.20 cost to compound gives a cost to manufacture of $0.749 per pound. Add a 30% markup for a price to the pallet molder of $1.07 per pound.

To provide 23% MDH in the final compound, 40 pounds of masterbatch will be used. So now we can compute the cost of raw materials. See Table App-VI-7.

Table App-VI-7. Raw Material Cost for a MDH FR PP Pallet using a PP FR Masterbatch

Formulation Component	**Loading**	**Cost/pound**	**Component Cost**
PP	58%	$1.00	$0.58
MDH-PP Masterbatch	40%	$1.07	$0.428
Black Masterbatch	1%	$2.00	$0.02
UV Thermal Concentrate	1%	$3.00	$0.03
Formulation Total Raw Material Cost/pound			$1.058

Let's look at specific gravity calculations for this non-halogen FR PP approach.

For the masterbatch, we have (let's leave out the process aid for this calculation):

PP at 0.28/0.9 sp grav = 0.3111 cc and MDH at 0.70/2.36 sp grav = 0.2966 cc for a total of 0.6077 cc/gram or 1.6455 grams per cc.

For the final MDH FR PP, we have:

PP at 0.58/0.9 sp grav = 0.6444
MDH Masterbatch at 0.4/1.6455 = 0.2431
Additives at 0.02/0.9 = 0.0222
Total = 0.9097 or 1/0.9097 = 1.0993 grams/cc (sp gravity)

So for a comparison, the density of the DECA containing iGPS HDPE pallet was 1.0312 while the density for our MDH FR PP pallet is 1.0993. So if iGPS or anyone else were to make a FR plastic pallet from our MDH FR PP formulation, the weight of that pallet in the same mold used for the iGPS pallet would be calculated as follows:

48.5 pounds x 1.0993/1.0312 = 51.7 pounds

Therefore, the non-halogen FR PP pallet made in the iGPS mold goes a little over the 50 pound mark (which is the recommended upper weight limit by the GMA).

What about using a phosphorus FR system in a plastic pallet?

The use of phosphorus flame retardants such as APP, APP derived compounds, and EDAP have not really found application in non-halogen FR plastic pallets, or many other applications for that matter. This is likely mostly due to first the fact that halogen FR's continue to be used and are cost/performance effective and secondly to a perception that phosphorus FR systems are just too costly. However, they may very well be worth taking a look at in a plastic pallet application since the flammability requirement, "burn like wood", is far lower than a more stringent requirement to be self-extinguishing. So let's take a look at the cost situation for EDAP as an example.

The cost for a typical FR PP formulation using EDAP , such as Unitex FR44-94S, that is expected to meet idle pallet requirements (this formulation has not been tested in this type of test as far as the authors know) would be calculated as in Table App-VI-8.

Table App-VI-8. Cost Calculation for an FR PP Formulation using EDAP

Formulation Component	**Loading**	**Cost/pound**	**Component Cost**
PP	86%	$1.00	$0.86
EDAP	12%	$2.50	$0.30
Stabilizers	2%	$2.50	$0.05
Formulation Total Raw Material Cost/pound			$1.21

With the $0.20/pound compounding cost and 30% profit, we have a cost to the pallet producer of $2.01/pound.

Specific gravity of EDAP is 1.3. The formulation specific gravity is:
PP at 0.86/0.9 sp grav = 0.9555
EDAP at 0.12/1.3 = 0.0923
Additives at 0.02/0.9 = 0.0222
Total = 1.07 or 1/1.07 = 0.9346 grams/cc (sp gravity)

A disadvantage of this system is that the EDAP compound cannot be introduced using a masterbatch but must instead be added during the compounding operation. (A second heat history is not a good thing when it comes to phosphorus compounds.) Recall that for the DECA and metal hydrate FR systems, a masterbatch can be used.

The same formulation might also work with HDPE as the resin. In such a case, the specific gravity of the formulation would be:

HDPE at 0.86/0.96 sp grav		= 0.8958
EDAP at 0.12/1.3		= 0.0923
Additives at 0.02/0.9		= 0.0222
	Total	= 1.0103 or 1/1.0103 = 0.99 grams/cc (sp gravity)

So what does all of this mean? It means that since the iGPS pallet weighs about 48.5 pounds and has a specific gravity of 1.0312 (see highlighted result on p. 24 above), then this HDPE-EDAP formulation with a specific gravity of 0.99 would produce a pallet that weighs 46.6 pounds. (48.5/1.0312 x 0.99)

The net result then is the iGPS pallet made using the DECA masterbatch would cost 48.5 pounds of material times the HDPE-DECA cost of $1.105/pound or $53.59. Whereas the HDPE-EDAP formula pallet weighs 46.6 pounds with a cost of material to the pallet producer of $2.01/pound or a price of $93.66. So herein lays the drawback to the phosphorus approach. The final cost is prohibitively high – at least in comparison to other options. The same problem occurs when considering APP with a specific gravity of 1.8 and a HDPE-APP formulation cost equivalent to the HDPE-EDAP cost of $2.01/pound. The pallet weight is slightly higher at about 47.8 pounds and the cost is still above $90 per pallet.

So in summary it seems logical to conclude that a non-halogen FR plastic pallet is going to have to start with a metal hydrate, probably magnesium hydroxide, and a polyolefin resin, probably PP. ATH could be used as well but temperatures must be kept low and so the resin with this FR must be HDPE (as PP is processed above the ATH water release temperature). Polypropylene is a little more costly on $/pound purchase price than HDPE, but hopefully we have now learned that the initial cost per pound has nothing to do with the cost of the material going into the mold. The cost and specific gravity calculations must be performed first to get a true picture of the cost to fill the pallet mold.

The exact formulation components and cost numbers in the real world will be different than those shown here because we have simplified the formulations to make it easier to understand the calculation principles and because prices fluctuate on a daily basis for almost all materials. The important thing to learn is that there is a lot involved in developing a balanced formulation. When flame retardants are loaded into formulations, especially those needing to meet more stringent flammability standards (more stringent than “burn like wood”), the physical property most impacted is tensile strength. The tensile strength goes down and translated to a pallet in use, this means it will be more likely to break under load. However, at the reduced FR loadings needed for a FR plastic pallet, the adverse impact on tensile strength as well as other properties is lessened considerably. (This helps support the argument that making a non-halogen FR plastic pallet is feasible.)

Appendix VII: Innovative and Novel Non-Halogen Flame Retardants

Nicholas A. Zaksek, Manager of Applications Research and Development, JJI Technologies
[Paper presented at ANTEC 2010 by David Diefenthal and sponsored by Society of Plastic Engineers]

Abstract

JJI Technologies bases its technology platform on developing innovative and novel non-halogen flame retardants and plastic additives. Our self-catalyzed technology embedded within the flame retardant enhances physical performance, increases extinguishing efficiency, and simplifies the compounding process. Our JJAZZ™ FR boasts features such as low smoke and odor when exposed to flame. This is achieved by forming a robust char barrier that stops the flame from propagating to the polyolefin. Features such as a low specific gravity, lower loading levels, and non-blooming help to exemplify the overall cost savings and improved aesthetics that benefit the user.

Introduction

The demands for flame retarded materials continues to increase with building material and electrical component markets pushing toward the use of polymers in increasing numbers of end applications. There are 3 basic constituents that must be considered when flame retarding polymers; the effectiveness of the flame retardant, the physical properties, and the sustainability of the product throughout its life cycle.

In most applications, the additions of non-halogen flame retardants are considered to be fillers as opposed to an additive. This is especially true in the case of metal hydroxides and hydrates where the loadings comprise of more than fifty percent of the polymer system. The addition of filler to a polymer often dramatically impacts the physical properties of the polymer. The effectiveness of the flame retardants to reduce flame spread, smoke generation, and in many cases extinguish the flame establishes its value in the market. The necessary loading of the flame retardant to meet the demands of stringent flame tests, also effects the latter. Finally, sustainability has become a rapidly increasing concern among plastic compound manufacturers as well as flame retardant producers. Regulations are driving initiatives to recycle and preserve the environment. The importance of “green” products has become more prevalent than ever before.

Flame retardants can no longer maintain a pristine image by proving safe in their usable form. They are scrutinized from the point of manufacturer, how safe they are for exposure to humans and pets, what by-products occur when they burn (i.e. toxic smoke, carcinogens), and their end of life. Bioaccumulation, decomposition products, heavy metals, small molecules, halogens, PBB and PBDE’s, and recyclability are all concerns that the new generations of flame retardants have

to answer too.[1] This paper serves to illustrate that through innovative knowledge and technology; JJI Technologies is developing and improving its flame retardant additives to meet the demands of the market and its customers.

JJAZZ Physical Properties

JJAZZ™ is a free flowing white powder available in three particle sizes to meet physical and dielectric application demands (Figure 1, 2). The powder is a neutral pH and exhibits a low specific gravity to reduce compound weight. With the lower loading levels needed to flame retard a compound, it is easy to color. The aesthetics of products are also enhanced since the JJAZZ™ does not exhibit any surface migration. All of the properties contribute to an efficient flame retardant that is non-toxic, generates less smoke, and is fully recyclable. A chart illustrates a full comparison of JJAZZ™ as well as other products JJI currently has in development (Figure 3).

Results and Discussion

Upon investigating traditional non-halogen flame retardants, metal hydroxide and hydrate flame retardants are limited due to the excessively high loading necessary to achieve acceptable performance results. These excessively high loadings significantly impact physical properties as well as adding weight to the final compound.[2] Intumescent flame retardants, like those in the ammonium polyphosphate family, allow loading levels to be reduced, thus preserving the properties of the base resin. Unfortunately, most of these flame retardants need a synergist, usually a pentaerythritol, which needs to be added congruently for the system to be fast-acting and completely effective. This synergist has proven to be the Achilles heel of these FR's due to it being hydrolytically weak coupled with the inability to insure full dispersion (Figure 4).[3]

Mechanisms

The reason for the addition of a synergist lies in the mechanism of how intumescent systems work. They are comprised of three components: an acid source (APP), a carbon source (pentaerythritol), and a blowing agent (typically melamine) which all need to interact with each other in a prescribed sequence of events[4, 5]. The acid source breaks down to dehydrate the carbon source. Once this process is complete; the blowing agent has to decompose in order to form a protective heat sink char[6].

JJAZZ™ not only utilizes the above method of action, but also reacts to form nitrogen gas to dilute the fuel source and prevent the acid source from volatizing away before it can react with the carbon source.

Char Formation

JJAZZ™ has overcome the hurdles noted above by embedding a proprietary catalyst to eliminate the need for the addition of a synergist. This self catalyzing technology ensures good distribution at a molecular level (Figure 5). This allows for superior distribution and functionality

within the polymer which decreases loading levels. Also this would improve the physical properties of the final product. The technology also serves two additional purposes; it creates low activation energy and a fast deploying char. JJAZZ™ also creates a dual layer char consisting of initially a hard and glassy char, accompanied by a porous and highly insulating char upon continued exposure to flame. This unique mechanism may require additional additives in a standard FR system. This is clearly illustrated by the two maximum decomposition point shown by TGA analysis (Figure 6).

JJAZZ™ Performance Data

All performance data will vary due to resin selection, the final application, and the additives package that is utilized in the compound. Several addition levels of JJAZZ™ were compounded on a 50mm twin screw extruder in a 7 melt flow rate polypropylene to illustrate the minimal impact JJAZZ addition has on the final compound. These loading levels are in accordance with tests that require more stringent and rigorous burn testing requirements. One additional note is that the melt flow rate was measured at a lower temperature in order to keep the FR from prematurely activating. The data is listed in a chart below (Figure 7).

Processing Parameters

JJAZZ™, like other phosphorous based FR's, does have processing limitations and is therefore limited to polyolefins and some rubber compounds. Typical processing temperatures on an extrusion unit should not exceed 390°F (~200°C). JJI Technologies provides support on proper extrusion parameters in order to achieve the optimal compound results (Figure 8, 9).

Continued R&D

It has been noted that not one flame retardant can fill every need. The key to success of the application is optimizing intumescent systems to react as near to the base resin decomposition point as possible. Various temperature ranges, as well as decomposition behavior of plastics and test methods dramatically affects how readily a compound can be flame retarded. This requires flame retardants to offer a variety of temperature ranges as well as extinguishing mechanisms to meet every market demand. JJI Technologies has a committed R&D effort to span this gap and diversify its product lines to not just meet, but exceed these demands (Figure 10). There is also an ongoing effort within JJI Technologies to innovate current technologies to enhance the robustness of our JJAZZ™ processing by increasing the temperature stability.

Figure 1. Dielectric properties of 2.5µm

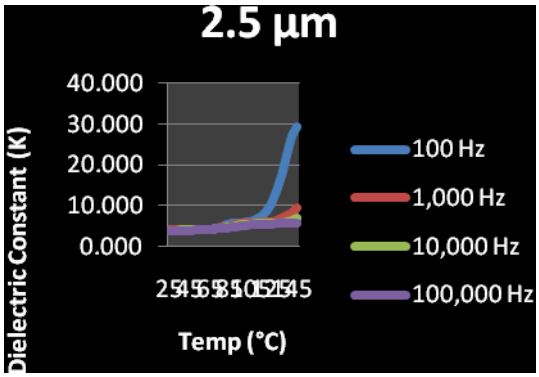


Figure 2. Dielectric properties of 6µm

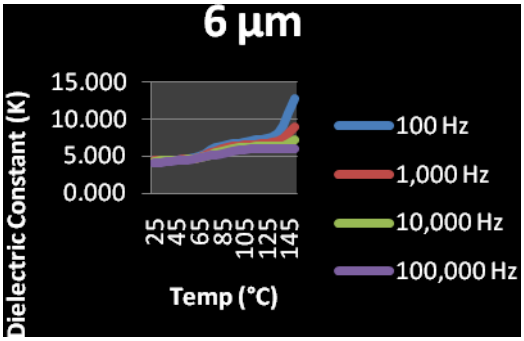


Figure 3. JJI product properties

Physical Property	JJAZZ®	*DP-110
Appearance	White Powder	White Powder
Decomposition Temp (2%, Nitrogen)	>230°C (464°F)	N/A
Activation Temp	~250°C (482°F)	~345°C (653°F)
Bulk Density	400	400
Phosphorus Content	15-17%	N/A
Nitrogen Content	>20%	N/A
pH	7.2	7.2
Specific Gravity	1.30	1.28

*DP-110 is in development

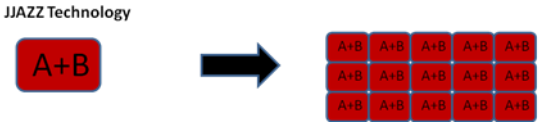
Figure 4. Conventional 2 component technology

*Gray indicates inactive

*An X indicates hydrolytically compromised

*Read and blue indicate active sites

Figure 5. JJAZZ™ single component technology



*All pairs are active

Figure 6. TGA and DSC analysis of char mechanism

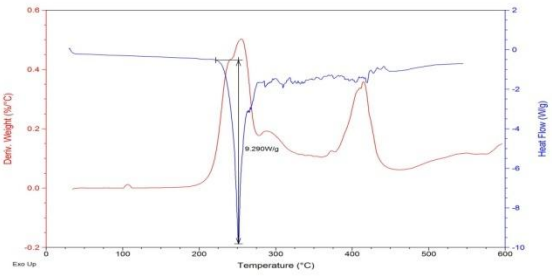


Figure 7. Performance Data

	Control	31% JJAZZ™	35% JJAZZ™	40% JJAZZ™
UL 94 1.6mm	**Fail**	**V2**	**V0**	**V0**
Specific Gravity	**0.901**	**1.04**	**1.02**	**1.03**
Hardness (Shore A)	**87.5**	**81.8**	**84.5**	**86.5**
MFI	**3.72**	**1.53**	**1.55**	**0.98**
Notch Izod	**7.857**	**1.243**	**1.101**	**1.079**
Tensile at Break	**2536**	**1906**	**1789**	**1709**
Elongation at Break	**51.21**	**66.61**	**51.52**	**30.72**
Flex Modulus	**173205**	**202987**	**217319**	**245448**

Units

- MFI (melt flow index) – (190°C/2.16kg)
- Notch Izod – (ft-lb/in)
- Tensile – (psi)
- Elongation – (%)
- Flex Modulus – (psi)

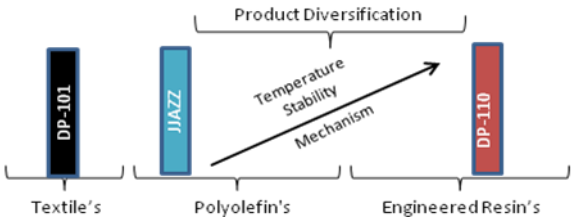
Figure 8. JJAZZ™ Processing Parameters

Die	Zone 5	Zone 4	Zone 3	Zone 2	Zone 1
380	370	340	340	350	350

Figure 9. Suggested extruder set-up

- 11 barrel extruder
- Ambient vent at barrel 6
- Side feeder at barrel 7
- Vacuum at barrel 10
- Pellet and powder in barrel 1
- A 1:2 feed ratio of powder from the rear feeder to the side feeder

Figure 10. Product Diversification



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5. Almeras, X., et al., *Structure and Morphology of an Intumescent Polypropylene Blend.* Journal of Applied Polymer Science, 2004. **93**: p. 402-411.
6. Ou. Yuxiang, *Technology of Flame Retardants.* Chemical Industry Publishing House, China. p. 205-207.

Appendix VIII: Plastics Flammability Tests: Smaller Scale Laboratory Tests

Prepared for this report by:
James Innes & Ann Innes
Flame Retardants Associates

UL 2335 and FM 4996 are the only tests for determining whether a flame retardant polymer pallet meets NFPA 13 requirements. But other tests are sometimes mentioned in the context of flame retardant plastics. Discussed below are smaller scale lab tests that often come up in discussion of fire resistant pallet testing. Some are actually more useful than others with regard to non-halogen fire resistant plastic pallets.

Testing with the Fire Propagation Apparatus

After a pallet has passed the FM 4996 test, any subsequent resin or formulation changes must be evaluated using the Fire Propagation Apparatus. If the results from this test are inconclusive, then full scale testing under the FM 4996 standard must be performed again. The Fire Propagation Apparatus is a piloted ignition open air test protocol using two 4 inch x 4 inch plaques or sheets of pallet material placed one on top of the other. The sample is exposed to external heat flux values up to 60 kW/m^2. Time to ignition is recorded along with other ignition-related data. To determine fire properties, the sample is exposed to radiant heat flux of 50 kW/m^2. Fire properties such as chemical heat release rate, mass loss rate, CO generation, and optical density of smoke are measured. This data is then used to judge if a formulation change must undergo the more costly full scale FM 4996 test protocol.

OI or LOI (Limiting Oxygen Index)

The OI or LOI test is a simple, small-scale test whose technical requirements are specified in ASTM D2863. This test measures the minimum amount of oxygen needed to support the burning process. The test is conducted in an oxygen/nitrogen atmosphere on 3 test specimens (6.5 mm wide strips of plastic) in a way that mimics candle-like burning conditions. Numerical results indicate the percentage of oxygen required to support burning of the sample. For example, a result of 28 means 28% of

the oxygen/nitrogen atmosphere was oxygen and this was the amount required to just support the burning process. (Oxygen is required for burning to take place. See FR101 in the next section.) Our atmosphere on planet Earth contains about 21% oxygen. So a result in the test of 28 indicates a good degree of flame retardancy. Theoretically, such a test specimen would resist burning in a real fire scenario as atmospheric oxygen does not reach a level of 28%. See Figure App-VIII-1 for the LOI test apparatus. ["Plastic Flame Retardants: Technology and Current Developments," J. Innes & A. Innes, Rapra Review Reports, 2003. P. 7]

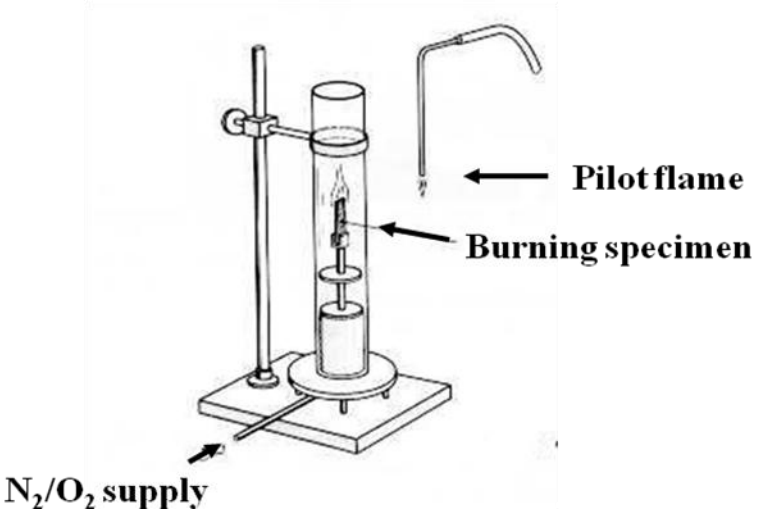

Figure App-VIII-1. LOI Test Apparatus

UL94 (Underwriters Laboratories)(Harmonized with ISO 9772, 9773)

Underwriters Laboratories UL94 test, Test for Flammability of Plastic Materials for parts in Devices and Appliances or Standard for Safety of Flammability of Plastic Materials for Parts in Devices and Appliances Testing, is perhaps the most well known flame retardant (FR) test in the industry. It has been and still is widely used for a variety of plastic materials which end up in an even wider variety of applications. This test together with UL746 A-C tests form the basis for the recognition of plastics as summarized in UL's Recognized Components Directory. UL94 applies to electrical parts, appliances, consumer and office equipment as well as other application areas *except* the use of

plastics in buildings. [“Plastics Flammability Handbook,” Jurgen Troitzsch, Carl Hanser Verlag, 2004, p. 533]. The UL94 standard actually contains several test protocols. The most common involves a vertical burn method and bar-shaped test specimens (13 mm x 125 mm of varying thicknesses such as 1/8”, 1/16”, 1/32”). The test bar is suspended a specified distance above a lump of cotton while a calibrated burner flame is applied to the specimen for 10 seconds, burn time of the specimen after removal of the flame is recorded, then the flame is applied to the specimen a second time for 10 seconds, and the burn time is again recorded. This procedure is followed for a set of five test bars. Performance in the test is indicated by burn time (usually in seconds) for each specimen, total after-flame burn time for all specimens, afterglow time, and the existence of flaming drips which may ignite the cotton. See Figure App-VIII-2 for the UL94 test apparatus sketch and Table App-VIII-1 for the UL94 test classification criteria. The result is actually expressed in this protocol as UL94 V0, V1, or V1 plus the thickness of the tested specimen. [“Plastic Flame Retardants,” Innes & Innes, p. 7.]

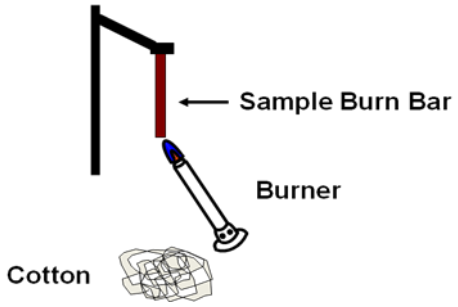

Figure App-VIII-2. UL 94 Test Apparatus

Table App-VIII-1. UL94 Materials classification (vertical burn test procedure)

Criteria	**UL94 V0**	**UL94 V1**	**UL94 V2**
Afterflame time for each individual specimen t_1 or t_2	≤ 10 s	≤ 30 s	≤ 30 s
Total afterflame ($t_1 + t_2$) for set of 5 specimens	≤ 50 s	≤ 250 s	≤ 250 s
Afterflame + Afterglow time ($t_2 + t_3$) for each specimen	≤ 30 s	≤ 60 s	≤ 60 s
Afterflame or Afterglow of any specimen up to clamp	No	No	No
Cotton indicator ignited by flaming drips	No	No	Yes

The other UL94 test protocols actually result in additional ratings including 5V (the highest flammability performance), HB (the lowest), as well as three other classifications each for horizontally burned specimens and very thin film specimens.

ASTM E2058-09 (Fire Propagation Apparatus)

ASTM's "Standard Test methods for Measurement of Synthetic Polymer Material Flammability Using a Fire Propagation Apparatus" actually uses flames from the burning material itself to characterize fire behavior. Laboratory measurements include heat release taken during upward fire propagation and burning on a vertical test specimen in specific atmospheres (normal air, oxygen rich, and/or oxygen partially depleted). Other measurements include time to ignition, chemical and convective heat release rates for horizontal specimens, mass loss rate and effective heat of combustion. [ASTM E2058-09]. This is the same apparatus referred to for testing the effects of any formulation changes to an FM 4996-approved pallet described above.

ASTM E1354 (ISO 5660) Cone Calorimeter

Unlike some of the above long-lived lab tests, the cone calorimeter is a comparatively newer test used to evaluate and measure rate of heat release of a burning test specimen. In ASTM 1354 (ISO 5660) Standard Test Method for Heat and Visible Smoke Release Rates for Materials and Products Using an Oxygen Consumption Cone Calorimeter, peak and total heat release rates as well as combustion gas composition are assessed in this test and used to characterize the tested materials. See Figure App-VIII-3 for a sketch of the apparatus.

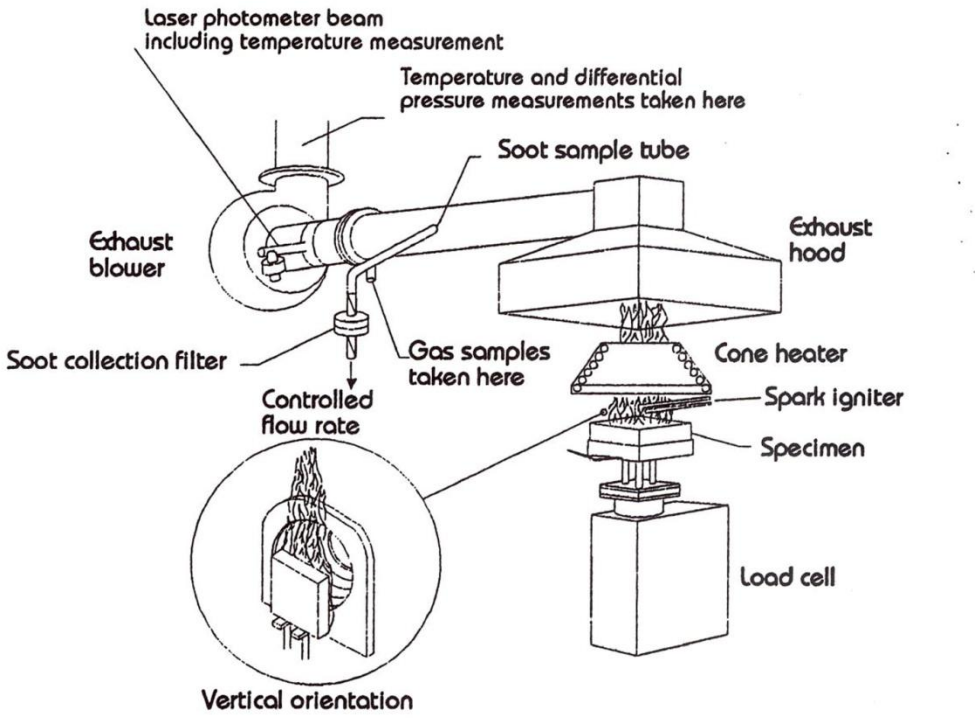

Figure App-VIII-3. Cone Calorimeter Apparatus sketch (Drawing by NIST) (23)

The actual test report includes a total of 24 reported items such as Time to Sustained Flaming (seconds), Heat Release Rate per unit area curve (kW/ms^2), Peak and Average Heat Release Rates for 60 seconds, 180 seconds, and 300 seconds after ignition (kW/m^2), Sample Mass Loss (kg/m^2), Smoke Obscuration (average extinction area m^2/kg), and if properly equipped measurements of other combustion gases are also included. [ASTM E1354-04a]

In the authors' opinion, the cone calorimeter and the FM heat release or fire propagation apparatus are the best and possibly the only good test to use in screening a formulation for application in FR plastic pallet. The ultimate requirement in both the FM and UL idle pallet flammability testing is to prove the FR plastic pallet is "like wood" or better. The smaller lab tests like UL94, LOI, etc, are all designed to indicate flame out, not continued burning "like wood". In the cone calorimeter, when wood is evaluated the peak rate of heat release is between 300-325 kW/m^2 at 50 kW incident heat. This value provides a benchmark for evaluation of any FR plastic formulation in comparison to wood.

Readers are cautioned that when evaluating in the cone, one flame retardant system can not necessarily be compared to a different flame retardant system. Allowances must be made for differences in fire retardancy mechanism.

The FM Fire Propagation Apparatus could also be used for screening purposes. However, a baseline must be established and the authors have been unable to locate such a baseline in the available literature.

Appendix IX

GREEN SCREEN ALTERNATIVES ASSESSMENTS FOR NINE FLAME RETARDANTS

November 30, 2010

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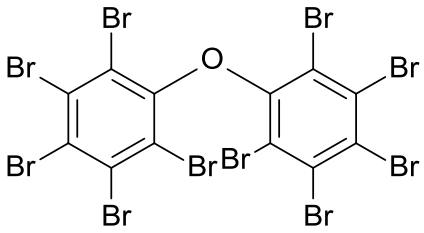
APPENDIX IXB: GREEN SCREEN FOR DECABROMODIPHENYL ETHER (CAS #1163-19-5)[2]

Also Called: 1,1'-Oxybis(2,3,4,5,6-pentabromobenzene), 1-06-00-00108 (Beilstein Handbook Reference), AFR 1021, AI3-27894, Adine 505, BDE 209, BDE-209, BR 55N, BRN 2188438, Berkflam B 10E, Bis(pentabromophenyl) ether, Bis(pentabromophenyl)ether, Bromkal 82-0DE, Bromkal 83-10DE, CCRIS 1421, Caliban F/R-P 39P, DB 10, DB 101, DB 102, DE 83, DP 10F, De 83R, Decabrom, Decabromdiphenyl oxide, Decabromobiphenyl ether, Decabromobiphenyl oxide, Decabromodiphenyl ether, Decabromodiphenyl oxide, Decabromophenyl ether, EB 10, EB 10FP, EB 10W, EB 10WS, EBR 700, EINECS 214-604-9, Ether, decabromodiphenyl, F/R-P 53, FR 10, FR 10 (ether), FR 300, FR 300BA, FR-PE, FR-PE(H), FRP 53, Fire Cut 83D, Flame Cut 110R, Flame Cut Br 100, HSDB 2911, NCI-C55287, NSC 82553, Nonnen DP 10, Nonnen DP 10(F), PBED 209, Pentabromophenyl ether, Planelon DB, Planelon DB 100, Planelon DB 101, Plasafety EB 10, Plasafety EBR 700, Saytex 102, Saytex 102E, Tardex 100

Chemical Structure of Decabromodiphenyl Ether:



For Inorganic Chemicals:
Define Form & Physiochemical Properties

1. Particle size (e.g. silica of respirable size) – n/a
2. Structure (e.g. amorphous vs. crystalline) – microcrystalline (NTP 1986)
3. Mobility (e.g. Water solubility, volatility) – 0.1 µg/L at 25˚C (Leisewitz 2000)

Identify Applications/Functional Uses: Flame retardant

Green Screen Rating[3]: Decabromodiphenyl ether was assigned a Benchmark Score of 1 based on a very High persistence (P) rating and High toxicity ratings for both acute (AA) and chronic (CA) aquatic toxicity (1c).

Green Screen (Version 1) Levels of Concern for Decabromodiphenyl Ether														
Human – Tier 1					Human – Tier 2				Eco		Fate		Physical	
C	M	R/D	ED	N	AT	Cr	Sn	ST	AA	CA	P	B	Ex	F
M	L	M	M	M	L	M	L	M	H	H	vH	M	nd	L

*Endpoints in italics were assigned using estimated values and professional judgment (Structure Activity Relationships).

[2] CPA recommends independent third-party validation of all Green Screen assessments. No independent third-party validation has been done for this assessment . Companies may not make marketing claims based on a Green Screen assessment that has not undergone an independent validation.

[3] For inorganic chemicals with low human and ecotoxicity across all hazard endpoints and low bioaccumulation, persistence alone will not be deemed problematic. Inorganic chemicals that are only persistent will be evaluated under the criteria for Benchmark 4.

Transformation Products and Ratings:
Identify relevant fate and transformation products (i.e., dissociation products, transformation products, valence states) **and/or moieties of concern**[4]

Life Cycle Stage	Transformation Pathway	Transformation Products	CAS #	Green Screen Rating
End of Life	UV Degradation	Low brominated diphenyl oxides	Multiple	n/a
End of Life	UV Degradation	PentaBDE	32534-81-9	PBT (CPA 2009)
End of Life	Combustion	Dioxin	1746-01-6	PBT, Carcinogen, Reproductive/Developmental Toxicant, Neurotoxicant, Endocrine Disruptor (CPA 2009)
End of Life	Combustion	Furan	110-00-9	Carcinogen (CPA 2009)
End of Life	Combustion	Carbon dioxide	124-38-9	Not present on the Red List of Chemicals (CPA 2009)
End of Life	Combustion	Carbon monoxide	630-08-0	Reproductive/Developmental Toxicant, Neurotoxicant (CPA 2009)
End of Life	Combustion	Hydrogen bromide	10035-10-6	Not present on the Red List of Chemicals (CPA 2009)

*The above transformation products were screened against the CPA's table of Red List chemicals.

Introduction

Decabromodiphenyl oxide ("DecaBDE" or "Deca") is an additive flame retardant used in a wide range of polymers including high impact polystyrene, engineering thermoplastics, and textile coating (Leieswitz 2000). DecaBDE has low water solubility (0.1 µg/L at 25˚C) and a log K_{ow} of > 5, which indicates a tendency to bioaccumulate. DecaBDE targets the liver, kidneys, spleen, and fat (Leieswitz 2000). The general population may be exposed to decaBDE via inhalation of ambient air, ingestion of fish, and dermal contact with products such as television or computer enclosures or textiles containing decaBDE (HSDB 2010). Studies have shown that all polybrominated diphenyl ethers (PBDEs) bioaccumulate in the environment and that the accumulation is inversely proportional to the degree of bromination (Darnerud 2001). Once in the environment, PBDEs biomagnify in the food chain. Because PBDEs accumulate in fat tissue, high levels of these compounds have been found in fatty fish.

[4] A moiety is a discrete chemical entity that is a constituent part or component of a substance. A moiety of concern is often the parent substance itself for organic compounds. For inorganic compounds, the moiety of concern is typically a dissociated component of the substance or a transformation product.

DecaBDE is most commonly used as a flame retardant. It is the most common of all polybrominated diphenyl ethers (NAS 2000). The major impurities are isomers of nonabromodiphenyl oxide and octabromodiphenyl oxide. The flame retardant mixture consists of approximately of 66-75% decaBDE and 25-33% antimony trioxide, a synergist (NAS 2000).

Recently, several U.S. states have placed bans on the manufacture or distribution of products containing decaBDE (OECD 2008). The European Union has requested a voluntary reduction program of decaBDE by manufacturers. Under An Act to Clarify Maine's Phaseout of Polybrominated Diphenyl Ethers (Public Laws 2009, chapter 610 [PL 2009, c. 610]), the Maine Department of Environmental Protection (DEP) is currently prohibiting the sale of shipping pallets containing decaBDE unless the pallet is made from recycled shipping pallets or unless an exemption has been granted by the Commissioner of Environmental Protection. The act additionally prohibits the replacement of decaBDE in pallets with other brominated or chlorinated flame retardants. DecaBDE has also been banned from being used in the manufacturing of mattresses and home furniture in Maine and California (OECD 2008).

Human Health – Tier 1

Carcinogenicity (C) Score (H, M or L): M

DecaBDE was assigned a score of Moderate for carcinogenicity based on evidence suggesting the chemical may be carcinogenic in humans and animals.

- DecaBDE has been assigned the following EU risk phrase: R40- Limited evidence of a carcinogenic effect (Physchem 2003).
- Feeding 3,500 to 7,000 mg/kg-bw to mice and 1,200 to 2,400 mg/kg-bw to rats suggests an elevated risk of cancer in the liver, pancreas, thyroid gland as well as an increased risk of leukemia (Leisewitz 2000).
- There is a reported increase in incidence of gullet cancer, rectum carcinoma, and duodenal cancer in decaBDE-exposed workers. However, due to contradictory results, the NTP and IARC have yet to classify decaBDE for carcinogenicity (Leisewitz 2000).
- Groups (50/sex/dose) of F344/N rats and B6C3F1 mice that were fed decaBDE (94–97% pure) at dietary concentrations of 0, 25,000, or 50,000 ppm for 103 weeks (equivalent to 1120, 1200, and 2240 mg/kg-d in male rats; 1120, 1200, and 2550 mg/kg-d in female rats; 3200, 3760, and 6650 mg/kg-d in male mice; and 3200, 3760, and 7780 mg/kg-d in female mice, respectively) Incidences of liver neoplastic nodules were significantly increased in low- and high-dose male rats (7/50 and 15/49, respectively, compared to 1/50 in controls) and high-dose female rats (9/50 compared to 1/50 and 3/49 in control and low-dose groups, respectively); this lesion appeared to be compound related. Incidence of hepatocellular carcinomas was low in all rat groups and apparently not compound related. There was a positive trend in mononuclear cell leukemia in male rats (30/50 controls, 33/50 low-dose rats, 35/50 high-dose rats), but the increase was marginal and not considered to be biologically significant because of the unusually high incidence in controls. A significant positive trend and marginally

greater incidence of acinar cell adenomas in the pancreas of high-dose male rats were also observed, but this lesion was considered to not be compound related. Hepatocellular adenomas or carcinomas (combined) were significantly increased in low- and high-dose male mice (8/50 controls, 22/50 low-dose mice, 18/50 high-dose mice). The incidence of hepatocellular carcinomas alone was significantly elevated in male mice in the low-dose group, but not in the high-dose group, as compared with controls. Thyroid gland follicular cell adenomas or carcinomas (combined) were marginally, but not significantly increased in male mice (0/50 controls, 4/50 low-dose mice, 3/50 high-dose mice). The possible significance of this finding was strengthened by increased incidences of follicular cell hyperplasia in the male mice (2/50 controls, 10/50 low-dose mice, 19/50 high-dose mice), but was weakened by increased mortality in control animals. There was no evidence of carcinogenicity in the female mice at either dose. The study concluded that there was "some evidence of carcinogenicity" for male and female rats based on significantly increased incidences of neoplastic nodules of the liver, and "equivocal evidence of carcinogenicity" for male mice based on a significantly increased incidence of hepatocellular tumors in only the low-dose group and non-statistically significant increases in thyroid follicular cell tumors in both dose groups. The conclusion of "some evidence of carcinogenicity" in rats appears to be based on the finding that the only chemical related effect was benign liver neoplasms. The conclusion of "equivocal evidence of carcinogenicity" in male mice appears to be based on the interpretation that the increases in liver and thyroid tumors are marginal and chemical related (NTP 1986).

Mutagenicity (M) and Genotoxicity Score (H, M or L): L

DecaBDE was assigned a score of Low for mutagenicity based on negative results from several genotoxicity assays.

- DecaBDE tested negative for mutagenicity in *Salmonella typhimurium* tester strains TA 100, TA 1535, TA 1537, and TA 98 at concentrations of 0, 100, 333, 1,000, 3,333, and 10,000 µg/plate with and without metabolic activation (NTP 1986).
- DecaBDE did not induce mutations in mouse L5178Y lymphoma cells with and without S9 at doses of 7, 8, 9, and 10 µg/mL (NTP 1986).
- DecaBDE did not induce sister-chromatid exchanges in Chinese hamster ovary cells both in the presence and absence of S9 at doses of 50, 100, 250, and 500 µg/mL (NTP 1986).
- DecaBDE did not induce chromosomal aberrations in Chinese hamster ovary cells at concentrations of 50, 100, 250, and 500 µg/mL in the presence and absence of S9 (NTP 1986).

Reproductive (R) and Developmental (D) Toxicity Score (H, M or L): M

DecaBDE was assigned a score of Moderate for reproductive and developmental toxicity based on the following risk phrase- R63.

- DecaBDE has been assigned the following EU risk phrase: R63- Possible risk of harm to the unborn child (Lookchem 2008).

- Male (10-15/dose) and female (20-30/dose) Sprague-Dawley rats were administered decaBDE (77.4% pure) daily for 60 days pre-mating, mating, gestation, and lactation for a total of approximately 115 days. Doses were 0, 3, 30, and 100 mg/kg. The reproductive NOAEL was 100 mg/kg (NAS 2000).
- Female rats (strain and number of animals not reported) were administered decaBDE (77.4% pure) at doses of 0, 10, 100, and 1,000 mg/kg on gestation days 6 through 15 via gavage in corn oil. No maternal toxicity or fetal malformations were observed. Subcutaneous edema and delayed skull ossification in pups was observed at 1,000 mg/kg. The maternal NOAEL was 1,000 mg/kg. The fetal NOAEL was 100 mg/kg and the LOAEL was 1,000 mg/kg (NAS 2000).
- Sprague-Dawley rats (25 mated females per dose group) were administered decaBDE in corn oil by gavage at doses of 0, 100, 300, or 1,000 mg/kg-day during gestation days 0 through 19. Dams were sacrificed on day 20 of gestation, and liver weights, gravid uterine weights, and the number of corpora lutea, implants, fetuses, and resorptions were recorded. The placenta and fetuses were examined for gross abnormalities, and histologic examinations were performed. All dams survived decaBDE treatment until scheduled sacrifice. There were no adverse treatment-related effects observed in maternal clinical findings, body weight, or body-weight gain. Although a slight but statistically significant increase in food consumption was observed at 1,000 mg/kg-day at time intervals up to day 12 of gestation, the authors did not consider this indicative of an adverse effect of treatment. No statistically significant differences were observed in maternal absolute or relative liver weights between treatment and control groups. At necropsy, gross examination of the dams revealed no adverse effect of treatment with decaBDE. Number of dams with viable fetuses, mean number of corpora lutea, number of implantation sites, percent preimplantation loss per dam, number of viable fetuses, and gravid uterine weights were not adversely affected by decaBDE treatment. A statistically significant increase in the mean number of early resorptions per dam was observed in the 1,000 mg/kg-day group compared to controls. Based on the lack of a consistent dose response for this effect (the mean number of early resorptions per dam was 0.6, 0.6, 0.5, and 1.4 at 0, 100, 300, and 1,000 mg/kg-day, respectively), lack of a statistically significant positive trend associated with the effect, and the historically high incidence of this effect (0.5–1.4) for the laboratory, these effects are not considered to be of toxicological significance. Examination of the results indicated a marginal increase in the postimplantation loss/dam of 7 and 9% at 300 and 1,000 mg/kg-day, respectively, compared with 4% in controls and at 100 mg/kg-day. However, this effect was not associated with a statistically significant positive trend. A slight, but statistically not significant, decrease in the percentage of viable fetuses per implant was seen (96, 96, 93, and 91% in the control, 100, 300, and 1,000 mg/kg-day groups, respectively). Fetal body weights, crown-rump ratio, and fetal sex ratio were not different between treatment and control groups. No adverse decaBDE treatment-related effects were identified during fetal external, skeletal, or visceral examinations. DecaBDE treatment, therefore, did not produce any evidence of maternal or developmental toxicity up to the highest dose tested of 1,000 mg/kg-day. The NOAEL for maternal and developmental toxicity in this study was 1,000 mg/kg-day, the highest dose tested (IRIS 2008).

Endocrine Disruption (ED) Score (H, M or L): M

DecaBDE was assigned a score of Moderate for endocrine disruption based on the chemical being listed as a potential endocrine disruptor.

- DecaBDE is listed as a potential endocrine disruptor on the EU Priority List of Suspected Endocrine Disruptors.
- DecaBDE is not listed as a potential endocrine disruptor on the OSPAR List of Chemicals of Possible Concern.
- DecaBDE is listed as a potential endocrine disruptor on the Red List of Chemicals (CPA 2009).
- There is suggestive evidence of hypothyroidism in a small number of workers occupationally exposed to decaBDE (ADSTR 2004).
- Long-Evans female rats (eight animals/dose group) were orally administered decaBDE (>98% purity) in corn oil at doses of 0, 0.3, 1, 3, 10, 30, 60, or 100 mg/kg-day for 4 consecutive days. Body weights were recorded and dosing volumes adjusted daily. Animals were sacrificed 1 day after the last dose. Serum total thyroxine (T4) and triiodothyronine (T3), serum thyroid stimulating hormone (TSH), and hepatic enzyme activities (EROD, a marker for CYP-1A1; PROD, a marker for CYP-2B1; and T4-uridine diphosphate glucuronyl transferase [T4-UDPGT]) were measured. Short-term treatment with decaBDE did not cause any visible signs of toxicity or any effects on body-weight gain or liver-to-body-weight ratios at any dose level. DecaBDE (up to 100 mg/kg-day) had no effect on serum T4, T3, or TSH concentration or on hepatic UDPGT activity. Based on these observations, the highest dose of 100 mg/kg-day is identified as the NOAEL (IRIS 2008).

Neurotoxicity (N) Score (H, M or L): M

DecaBDE was assigned a score of Moderate for neurotoxicity based on beings listed as a potential neurotoxicant on the Red List of Chemicals and based on an animal study that suggests decaBDE caused a decrease in activity.

- Not classified as a developmental neurotoxicant (Grandjean and Landrigan 2006).
- DecaBDE is listed as a potential neurotoxicant on the Red List of Chemicals (CPA 2009).
- The neurotoxic effects of decaBDE on spontaneous motor behavior of NMRI male mice were investigated in adult animals exposed to a single oral dose as neonates. Uptake of radiolabel by the brain of the neonatal mice orally administered 14C-labeled decaBDE on PND 3, 10, or 19 (i.e., at different stages of neonatal mouse brain development) was also measured to determine if there were age-related differences in tissue toxicokinetics that might correlate with the neurodevelopmental effects evaluated. In this behavioral study, 3-day-old and 19-day-old male mice were given a single dose of 0, 2.22, or 20.1 mg/kg body weight decaBDE (purity estimated to be >99%) in a 20% (weight/weight) emulsion vehicle of egg lecithin-peanut oil and water. Ten-day-old mice received 0, 1.34, 13.4, or 20.1 mg/kg. The spontaneous behavior test (measuring locomotion, rearing, and total activity) was conducted in 10 mice randomly selected from the litters in each treatment group at 2, 4, and 6 months of age. Treatment with decaBDE caused no clinical signs of toxicity at any time during the experimental period. Body weight and body-weight gain were not significantly different

between decaBDE- and vehicle-treated mice in the three different age groups. Control mice treated on PND 3, 10, or 19 exhibited normal habituation profiles. Pair-wise testing between adult mice exposed to 20.1 mg/kg on PND 3 and control groups indicated significant changes in all three spontaneous behavior variables at 2, 4, and 6 months of age. For the first 20 minutes, mice receiving 20.1 mg/kg displayed significantly less activity for locomotion, rearing, and total activity compared with controls. During the third 20-minute period, exposure of mice to 20.1 mg/kg on PND 3 caused significantly more activity for locomotion, rearing, and total activity than the controls at 2, 4, and 6 months. The only effect noted in mice exposed to 2.22 mg/kg was a significant decrease in total activity in the first 20-minute test period compared with the controls at 2 months of age. However, total activity returned to control level during the third 20-minute period. The lower dose of 2.22 mg/kg did not elicit any significant differences in these three variables compared with controls at 4 months of age. Lower activity was observed at 2.22 mg/kg during the first 20-minute period for the rearing variable at 6 months of age compared with controls, again returning to control level during the third 20-minute period. Mice exposed neonatally up to 20.1 mg on either PND 10 or 19 did not show any significant differences in any of the variables after 2, 4, or 6 months compared with controls. The authors indicated that the absence of effects on spontaneous activity in mice treated on PNDs 10 and 19 suggests that there is a critical window for the induction of the observed behavioral disturbances. The NOAEL in this study was 2.22 mg/kg, and the LOAEL was 20.1 mg/kg for significant changes in spontaneous motor behavior and decreased habituation capability for locomotion, rearing, and total activity, worsening with increasing age (IRIS 2008).

Human Health – Tier 2

Acute Mammalian (AT) Toxicity Score (H, M or L): L

DecaBDE was assigned a score of Low for acute mammalian toxicity based on oral and dermal LD_{50} values greater than 2,000 mg/kg-bw. Data is from three different routes of exposure in two different species of animals.

- DecaBDE has low acute oral toxicity because it is poorly absorbed from the gastrointestinal tract (NAS 2000).
- *Oral*: An LD_{50} of > 2,000 mg/kg was determined in the rat (ESIS 2000).
- *Oral*: An LD_{50} of > 5,000 mg/kg was determined in the rat (ESIS 2000).
- *Dermal*: An LD_{50} of > 2,000 mg/kg was determined in the rabbit (ESIS 2000).
- *Inhalation*: An LC_{50} of > 48.2 mg/L was determined in the rat (ESIS 2000).
- *Inhalation*: No deaths occurred in groups of 5 male and 5 female rats chamber-exposed to decaBDE dust mixture at concentrations as high as 48,200 mg/m^3 for 1 hour and observed the following 14 days (ATSDR 2004).

Corrosion/ Irritation (Skin/ Eye) (Cr) Score (H, M or L): M

DecaBDE was assigned a score of Moderate for corrosion and irritation based on the following risk phrases: R36, R37, R38.

- DecaBDE has been assigned the following EU risk phrases: R36- Irritating to eyes, R37- Irritating to respiratory tract, R38- Irritating to skin (Physchem 2003).
- Although animal studies have shown decaBDE to not be corrosive or irritating, occupational reports have suggested the substance produces skin and eye irritation (Leisewitz 2000).
- *Dermal*: DecaBDE caused essentially no dermal response in rabbits when applied as a dry solid (500 mg) to intact shaved skin under occluded conditions for 24 hours, and a slight erythematous and edematous response when similarly applied to abraded skin. Repeated application of dry solid decaBDE (500 mg) to intact skin of rabbits for 5 days/week for 2 weeks or to abraded skin for 3 days also did not alter their dermal responses (NAS 2000).
- *Dermal*: An acnegenesis study was performed in which 0.1 mL of 0.1%, 1%, 10%, or 100% decaBDE (0.40 mg/kg) in chloroform was rubbed into the external ear canal of four rabbits/dose level once a day, 5 days/week for 4 weeks. Observations made prior to the initial dose and after 7, 14, 21, and 28 days of dosing showed slight erythema, epidermal sloughing and scaling (effect levels not specified), but no clear indication of chloracne (a slight response was observed in one animal at the 10% concentration on day 28). Gross necropsy showed no treatment-related systemic effects. Other studies similarly reported that a 10% chloroform solution of decaBDE caused slight erythema and exfoliation, and no indication of chloracne, when applied to the ear of rabbits for 28 days. Other industry studies also found that 10% decaBDE in chloroform did not induce chloracne in rabbits (NAS 2000).
- *Ocular*: Ocular exposure to dry solid decaBDE caused transient conjunctival irritation in washed and unwashed rabbit eyes. Instillation of decaBDE (100 mg/eye) into the eye caused very slight conjunctival redness and chemosis and slight or moderate discharge in some rabbits, but the investigators concluded that the effects were not serious enough to be considered primary eye irritation. Other studies similarly reported that decaBDE did not cause primary eye irritation when instilled once (100 mg/eye) into the eye of rabbits (NAS 2000).
- *Ocular*: Rats (strain and number not reported) that were chamber-exposed to decaBDE dust at concentrations of 48,200 mg/m3 for one hour showed signs of eye squint, erythema, and/or ocular discharge (ADSTR 2004).

Sensitization (Sn) Score (Skin and Respiratory) (H, M or L): L

DecaBDE was assigned a score of Low for sensitization based on negative results from human and animal studies.

- *Dermal*: DecaBDE does not appear to be a primary irritant based on observations from a skin sensitization study in humans and dermal irritation and acnegenesis studies in animals. A human skin sensitization study was conducted in which 0.03 mL of a 5% suspension of commercial decaBDE in petrolatum (0.02 mg/kg) was applied via patch to the skin of 50 subjects three times per week for 3 weeks. Commercial decaBDE was a mixture that contained 77.4% decaBDE, 21.8% nonaBDE, and 0.8% octoBDE. The dermal applications did not result in skin sensitization reactions during the sensitizing period or on challenge 2 weeks after the last application. Skin irritation, attributed to the stringency of the test procedure by the investigators, occurred in 9 of the 50 subjects (14/450 total

applications; 11 of the reactions were classified as very slight and 3 as mild erythema) (NAS 2000).

Systemic/ Organ (ST) Toxicity Score (includes organ effects and immunotoxicity) (H, M or L): M

DecaBDE was assigned a score of Moderate for systemic toxicity based on animal studies and the following risk phrases: R20, R21, R22, R48/20.

- DecaBDE has been assigned the following EU risk phrases: R20- Harmful by inhalation, R21- Harmful in contact with skin, R22- Harmful if swallowed (Physchem 2003) and R48/20- Danger of serious damage to health by prolonged exposure and harmful by inhalation (Lookchem 2008).
- DecaBDE will accumulate in the liver, kidneys, and fat tissue of animals (Leisewitz 2000).
- Rats (strain, sex, and number of animals not reported) were exposed to decaBDE at concentrations of 2,000 or 48,000 mg/m^3 via inhalation for 1 hour and then observed for 14 days. No deaths or effects on body weight were observed however, dyspnea and ocular porphyrin discharge were observed at both concentration levels and eye squint was observed in the high concentration level only (NAS 2000).
- Male Sprague-Dawley rats (5/dose) were administered oral doses of decaBDE (77.4% pure) at 0, 8, 80, and 800 mg/kg per day for 30 days. Clinical symptoms included thyroid hyperplasia at the 80 and 800 mg/kg dose levels, increased liver weight at 80 mg/kg, increased liver weight and pathology at 800 mg/kg, and renal tubular degeneration at 800 mg/kg. A NOAEL of 8 mg/kg-day and LOAEL of 80 mg/kg-day was assigned (NAS 2000).
- Male and female rats (10/dose, strain not reported) were administered decaBDE (purity not reported) orally in doses of 0, 7.4, or 74 mg/kg-day for 28 days. No histological liver or thyroid changes were observed and the NOAEL was established to be 74 mg/kg-day (NAS 2000).
- In a 2 year oral study, male and female Sprague-Dawley rats (25/dose) were administered decaBDE (77.4% pure) at concentrations of 0, 0.01, 0.1, or 1 mg/kg-day. No adverse effects were observed and the NOAEL was established to be 1 mg/kg-day (NAS 2000).
- Male and female F344/N rats (5/sex/dose) were fed diets containing 0, 5,000, 10,000, 20,000, 50,000, or 100,000 ppm decaBDE (99% purity) for 14 days. The corresponding estimated average daily doses were 0, 472, 928, 1,846, 4,569, or 9,326 mg/kg-day in male rats and 0, 538, 1,061, 2,137, 5,323, or 10,853 mg/kg-day in female rats. No mortality was observed in the rats during the course of the study. Exposure to decaBDE did not cause any clinical signs of toxicity or adversely affect the final mean body weights. Gross pathological effects were not noted in any animal at any dose level. The results of this study indicated a NOAEL of 9,326 mg/kg-day in male rats and 10,853 mg/kg-day in female rats (NTP 1986).
- The subchronic effects of decaBDE (97–99% purity) on rats were investigated in a 13-week study. Groups of F344/N rats (10/sex/dose) were administered decaBDE in the diet at concentrations of 0, 3,100, 6,200, 12,500, 25,000, or 50,000 ppm for 13 weeks. The corresponding estimated average daily doses were

0, 191, 372, 781, 1,536, or 3,066 mg/kg-day in male rats and 0, 238, 504, 967, 1,955, or 3,944 mg/kg-day in female rats. A necropsy was performed on all animals, including those killed in extremis, with the exception of those excessively autolyzed or cannibalized. Histologic examination was performed on major organs and tissues from control and high-dose groups. No mortality was observed in rats fed decaBDE, and no clinical signs of toxicity were noted. Compound-related changes in body weight and feed consumption were not observed, and no gross or macroscopic pathological effects were noted in any animal examined. The results indicate a NOAEL of 3,066 mg/kg-day in male rats and 3,944 mg/kg-day in female rats (NTP 1986).

- Male and female B6C3F1 mice (5/sex/dose) were fed diets containing 0, 5,000, 10,000, 20,000, 50,000, or 100,000 ppm decaBDE (99% purity) for 14 days. The estimated average daily doses were 0, 1,027, 2,143, 4,246, 10,536, or 20,994 mg/kg-day in male mice and 0, 1,146, 2,286, 4,627, 11,348, or 23,077 mg/kg-day in female mice. Necropsy was performed at the end of the exposure period, and several organs and tissues were examined histologically. Exposure to decaBDE up to 20,994 mg/kg-day in males and 23,077 mg/kg-day in females showed no effects on survival or body weight, and there were no clinical signs of toxicity. No compound-related gross pathological effects were noted in any animal in any group. The results of this study indicate a NOAEL of 20,994 mg/kg-day in male mice and 23,077 mg/kg-day in female mice (NTP 1986).
- B6C3F1 mice (10/sex/dose) were fed diets containing 0, 3,100, 6,300, 12,500, 25,000, or 50,000 ppm decaBDE (97–99% purity) for 13 weeks. The corresponding estimated average daily doses were 0, 666, 1,355, 2,659, 5,278, or 10,233 mg/kg-day in males and 0, 702, 1,437, 2,899, 5,687, or 11,566 mg/kg-day in females. Necropsy was performed on all animals, including those killed in extremis, with the exception of those excessively autolyzed or cannibalized. Histologic examination was performed on the organs and tissues from control and high-dose groups. Only one male and one female mouse fed 12,500 ppm died in the course of the study. There were no clinical signs of toxicity, and no compound-related effects on body weight and feed consumption were observed. No gross or macroscopic pathological effects were noted in any animal at any dose. The results of this study indicated a NOAEL of 10,233 mg/kg-day in males and 11,566 mg/kg-day in females (NTP 1986).

Ecotoxicity

Acute Aquatic (AA) Toxicity Score (H, M or L): H

DecaBDE was assigned a score of High for acute aquatic toxicity based on L/EC_{50} values less than 1 mg/L.

- An LC_{50} of > 500 mg/L was identified in killifish (freshwater fish, 48 hour) (ESIS 2000).
- ECOSAR – DecaBDE is designated to the neutral organics ECOSAR class. The estimated L/EC_{50} values are 9.4×10^{-7} mg/L (fish, 96 hr), 2.36×10^{-6} mg/L (daphnid, 48 hr), and 9.05×10^{-5} mg/L (algae, 96 hr) (U.S. EPA 2009).
- An EC_{50} of > 1 mg/L was identified in algae (ESIS 2000).

Chronic Aquatic (CA) Toxicity Score (H, M or L): H
DecaBDE was assigned a score of High for chronic aquatic toxicity based on ChV values less than 0.1 mg/L.

- DecaBDE has been assigned the following EU risk phrase: R50/53- Very toxic to aquatic organisms, may cause long term effects in the aquatic environment (Lookchem 2008).
- ECOSAR – The estimated ChV values are 6.06×10^{-7} mg/L (fish, 96 hr) and 1.36×10^{-6} mg/L (daphnid) (U.S. EPA 2009).

Environmental Fate

Persistence (P) Score (vH, H, M, or L): vH
DecaBDE was assigned a score of very High for persistence based on the chemical not being readily biodegradable and a half life in soil greater than 180 days and a half life in water greater than 60 days.

- BIOWIN predicts decaBDE will not readily biodegrade. STP removal expected using BIOWIN/EPA Draft Method results indicate 94.04% total removal, with 0.78% due to biodegradation. Fugacity modeling predicts 95.6% partitioning to soil with a half-life of 360 days, and 4.26% partitioning to water with a half-life of 180 days (U.S. EPA 2010).

Bioaccumulation (B) Score (vH, H, M, or L): M
DecaBDE was assigned a score of Moderate for bioaccumulation based on a BAF less than 500, and a log K_{ow} greater than 5, and degradation products that are likely to bioaccumulate.

- BCFBAF predicts a bioaccumulation factor (BAF) of 6.929 and a log K_{ow} of 12.11 (U.S. EPA 2010).

Physical Properties

Explosivity (Ex) Hazard Rating (H, M or L): nd

- No relevant data were identified for DecaBDE.

Flammability (F) Hazard Rating (H, M or L): L
DecaBDE was assigned a score of Low for flammability because no basis for concern was identified.

- DecaBDE is not flammable (ESIS 2000).

EPI Suite Results for Decabromodiphenyl Ether:

CAS Number: 1163-19-5
SMILES : O(c(c(c(c(c1Br)Br)Br)Br)c1Br)c(c(c(c(c2Br)Br)Br)Br)c2Br
CHEM : Benzene, 1,1 -oxybis[2,3,4,5,6-pentabromo-
MOL FOR: C12 Br10 O1
MOL WT : 959.17
---------- EPI SUMMARY (v4.00) ----------
Physical Property Inputs:
Log Kow (octanol-water): ------
Boiling Point (deg C) : ------
Melting Point (deg C) : ------
Vapor Pressure (mm Hg) : ------
Water Solubility (mg/L): ------
Henry LC (atm-m3/mole) : ------

Log Octanol-Water Partition Coef (SRC):
Log Kow (KOWWIN v1.67 estimate) = 12.11

Boiling Pt, Melting Pt, Vapor Pressure Estimations (MPBPVP v1.43):
Boiling Pt (deg C): 589.71 (Adapted Stein & Brown method)
Melting Pt (deg C): 254.50 (Mean or Weighted MP)
VP(mm Hg,25 deg C): 4.67E-012 (Modified Grain method)
VP (Pa, 25 deg C) : 6.23E-010 (Modified Grain method)
MP (exp database): 295 deg C
BP (exp database): 530 deg C
Subcooled liquid VP: 4.74E-009 mm Hg (25 deg C, Mod-Grain method)
: 6.32E-007 Pa (25 deg C, Mod-Grain method)

Water Solubility Estimate from Log Kow (WSKOW v1.41):
Water Solubility at 25 deg C (mg/L): 2.841e-011
log Kow used: 12.11 (estimated)
no-melting pt equation used
Water Sol (Exper. database match) = 0.0001 mg/L (25 deg C)
Exper. Ref: HARDY,ML & SMITH,RL (1999); < 0.1 ppb

Water Sol Estimate from Fragments:
Wat Sol (v1.01 est) = 2.5606e-006 mg/L

ECOSAR Class Program (ECOSAR v1.00):
Class(es) found: Neutral Organics

Henrys Law Constant (25 deg C) [HENRYWIN v3.20]:
Bond Method : 1.19E-008 atm-m3/mole (1.20E-003 Pa-m3/mole)
Group Method: 4.45E-008 atm-m3/mole (4.51E-003 Pa-m3/mole)
For Henry LC Comparison Purposes:
User-Entered Henry LC: not entered
Henrys LC [via VP/WSol estimate using User-Entered or Estimated values]:
HLC: 2.075E-001 atm-m3/mole (2.102E+004 Pa-m3/mole)
VP: 4.67E-012 mm Hg (source: MPBPVP)
WS: 2.84E-011 mg/L (source: WSKOWWIN)

Log Octanol-Air Partition Coefficient (25 deg C) [KOAWIN v1.10]:
Log Kow used: 12.11 (KowWin est)
Log Kaw used: -6.313 (HenryWin est)
Log Koa (KOAWIN v1.10 estimate): 18.423

Log Koa (experimental database): None

Probability of Rapid Biodegradation (BIOWIN v4.10):
Biowin1 (Linear Model) : -0.6806
Biowin2 (Non-Linear Model) : 0.0000
Expert Survey Biodegradation Results:
Biowin3 (Ultimate Survey Model): -0.3386 (recalcitrant)
Biowin4 (Primary Survey Model) : 1.0059 (recalcitrant)
MITI Biodegradation Probability:
Biowin5 (MITI Linear Model) : -0.2784
Biowin6 (MITI Non-Linear Model): 0.0001
Anaerobic Biodegradation Probability:
Biowin7 (Anaerobic Linear Model): 1.0141
Ready Biodegradability Prediction: NO

Hydrocarbon Biodegradation (BioHCwin v1.01):
Structure incompatible with current estimation method!

Sorption to aerosols (25 Dec C)[AEROWIN v1.00]:
Vapor pressure (liquid/subcooled): 6.32E-007 Pa (4.74E-009 mm Hg)
Log Koa (Koawin est): 18.423
Kp (particle/gas partition coef. (m3/ug)):
Mackay model : 4.75
Octanol/air (Koa) model: 6.5E+005
Fraction sorbed to airborne particulates (phi):
Junge-Pankow model : 0.994
Mackay model : 0.997
Octanol/air (Koa) model: 1

Atmospheric Oxidation (25 deg C) [AopWin v1.92]:
Hydroxyl Radicals Reaction:
OVERALL OH Rate Constant = 0.0337 E-12 cm3/molecule-sec
Half-Life = 317.534 Days (12-hr day; 1.5E6 OH/cm3)
Ozone Reaction:
No Ozone Reaction Estimation
Fraction sorbed to airborne particulates (phi):
0.996 (Junge-Pankow, Mackay avg)
1 (Koa method)
Note: the sorbed fraction may be resistant to atmospheric oxidation

Soil Adsorption Coefficient (KOCWIN v2.00):
Koc : 2.762E+005 L/kg (MCI method)
Log Koc: 5.441 (MCI method)
Koc : 4.78E+007 L/kg (Kow method)
Log Koc: 7.679 (Kow method)

Aqueous Base/Acid-Catalyzed Hydrolysis (25 deg C) [HYDROWIN v2.00]:
Rate constants can NOT be estimated for this structure!

Bioaccumulation Estimates (BCFBAF v3.00):
Log BCF from regression-based method = 1.620 (BCF = 41.71 L/kg wet-wt)
Log Biotransformation Half-life (HL) = 2.7638 days (HL = 580.5 days)
Log BCF Arnot-Gobas method (upper trophic) = -0.039 (BCF = 0.9147)
Log BAF Arnot-Gobas method (upper trophic) = 0.841 (BAF = 6.929)
log Kow used: 12.11 (estimated)

Volatilization from Water:

Henry LC: 4.45E-008 atm-m3/mole (estimated by Group SAR Method)
Half-Life from Model River: 4.075E+004 hours (1698 days)
Half-Life from Model Lake : 4.448E+005 hours (1.853E+004 days)

Removal In Wastewater Treatment:
Total removal: 94.04 percent
Total biodegradation: 0.78 percent
Total sludge adsorption: 93.26 percent
Total to Air: 0.00 percent
(using 10000 hr Bio P,A,S)

Removal In Wastewater Treatment:
Total removal: 94.04 percent
Total biodegradation: 0.78 percent
Total sludge adsorption: 93.26 percent
Total to Air: 0.00 percent
(using Biowin/EPA draft method)

Level III Fugacity Model:

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	0.114	7.62e+003	1000
Water	4.26	4.32e+003	1000
Soil	95.6	8.64e+003	1000
Sediment	0.00236	3.89e+004	0

Persistence Time: 7.26e+003 hr

ECOSAR Results for Decabromodiphenyl Ether:

SMILES : O(c(c(c(c(c1Br)Br)Br)Br)c1Br)c(c(c(c(c2Br)Br)Br)Br)c2Br
CHEM : Benzene, 1,1 -oxybis[2,3,4,5,6-pentabromo-
CAS Num: 001163-19-5
ChemID1:
ChemID2:
ChemID3:
MOL FOR: C12 Br10 O1
MOL WT : 959.17
Log Kow: 12.11 (KowWin estimate)
Melt Pt:
Wat Sol: 0.0001 mg/L (experimental database)

ECOSAR v1.00 Class(es) Found

Neutral Organics

ECOSAR Class	Organism	Predicted Duration	End Pt	mg/L (ppm)
Neutral Organics	: Fish	96-hr	LC50	9.4e-007
Neutral Organics	: Fish	14-day	LC50	1.12e-006
Neutral Organics	: Daphnid	48-hr	LC50	2.36e-006
Neutral Organics	: Green Algae	96-hr	EC50	9.05e-005
Neutral Organics	: Fish	30-day	ChV	1.93e-007
Neutral Organics	: Daphnid		ChV	1.36e-006
Neutral Organics	: Green Algae		ChV	0.000187 *
Neutral Organics	: Fish (SW)	96-hr	LC50	6.06e-007
Neutral Organics	: Mysid Shrimp	96-hr	LC50	6.92e-010

Neutral Organics	: Fish (SW)		ChV	4.57e-005
Neutral Organics	: Mysid Shrimp (SW)		ChV	2.99e-012
Neutral Organics	: Earthworm	14-day	LC50	149.184 *

Note: * = asterisk designates: Chemical may not be soluble enough to measure this predicted effect.

Neutral Organics:

For Fish LC50 (96-h), Daphnid LC50, Mysid: If the log Kow is greater than 5.0, or if the compound is solid and the LC50 exceeds the water solubility by 10X, no effects at saturation are predicted.

For Fish LC50 (14-day) and Earthworm LC50: If the log Kow is greater than 6.0, or if the compound is solid and the LC50 exceeds the water solubility by 10X, no effects at saturation are predicted.

For Green Algae Acute Toxicity Values: If the log Kow of the chemical is greater than 6.4, or if the compound is solid and the EC50 exceeds the water solubility by 10X, no effects at saturation are predicted for these endpoints.

For All Chronic Toxicity Values: If the log Kow of the chemical is greater than 8.0, or if the compound is solid and the ChV exceeds the water solubility by 10X, no effects at saturation are predicted for these endpoints.

ECOSAR v1.00 SAR Limitations:

Maximum LogKow: 5.0 (Fish 96-hr LC50; Daphnid LC50, Mysid LC50)
Maximum LogKow: 6.0 (Fish 14-day LC50; Earthworm LC50)
Maximum LogKow: 6.4 (Green Algae EC50)
Maximum LogKow: 8.0 (ChV)
Maximum Mol Wt: 1000

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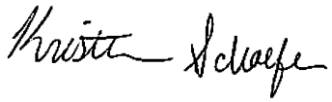
Decabromodiphenyl Oxide Green Screen Evaluation Prepared By:



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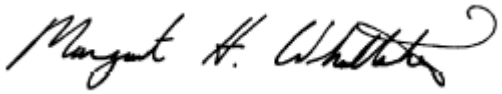
Decabromodiphenyl Oxide Green Screen Evaluation QC'd By:



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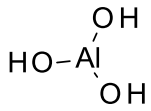
APPENDIX IX C: GREEN SCREEN FOR ALUMINUM TRIHYDROXIDE (CAS #21645-51-2)[5]

Also Called: Aluminum oxide trihydrate, Aluminum trihydroxide, Alumina trihydrate, Aluminic acid

Chemical Structure of Aluminum Trihydroxide:



For Inorganic Chemicals:
Define Form & Physiochemical Properties (Leisewitz 2001)
1. Particle size: 0.1-0.6 μm
2. Structure: Crystalline
3. Mobility: Insoluble in water; soluble in alkaline solutions, acid solutions

Identify Applications/Functional Uses: Flame retardant

Green Screen Rating[6]: Aluminum trihydroxide was assigned a Green Screen Benchmark Score of 2 based on very High persistence (P), Moderate neurotoxicity (N), Moderate systemic toxicity (ST), and Moderate corrosion/irritation (Cr) (2c).

Green Screen (Version 1) Levels of Concern for Aluminum Trihydroxide														
Human – Tier 1					Human – Tier 2				Eco		Fate		Physical	
C	M	R/D	ED	N	AT	Cr	Sn	ST	AA	CA	P	B	Ex	F
L	*L*	L	nd	M	L	M	L	M	L	*M*	vH	L	L	L

*Endpoints in italics were assigned using estimated values and professional judgment (Structure Activity Relationships).

[5] CPA recommends independent third-party validation of all Green Screen assessments. No independent third-party validation has been done for this assessment . Companies may not make marketing claims based on a Green Screen assessment that has not undergone an independent validation.
[6] For inorganic chemicals with low human and ecotoxicity across all hazard endpoints and low bioaccumulation, persistence alone will not be deemed problematic. Inorganic chemicals that are only persistent will be evaluated under the criteria for Benchmark 4.

Transformation Products and Ratings:
Identify relevant fate and transformation products (i.e., dissociation products, transformation products, valence states) and/or moieties of concern[7]

Life Cycle Stage	Transformation Pathway	Transformation Products	CAS #	Green Screen Rating
End of life	Dissociation	Al^{3+}	7429-90-5	Present on the Red List of chemicals (CPA 2009).
End of life	Dissociation	OH-	3352-57-6	Not present on the Red List of chemicals (CPA 2009).

*The above transformation products were screened against the CPA's table of Red List chemicals.

Introduction

Aluminum trihydroxide is an additive mineral flame retardant, filler, and an additive for fume reduction (Leisewitz 2001). Because it is a relatively weak-acting flame retardant, it must be utilized in large quantities, which limits its application area. In addition, aluminum trihydroxide decomposes at 200˚C which further limits its application and cannot be used in plastics with high processing temperatures.

Aluminum trihydroxide is primarily used in the manufacturing of glass, ceramics, activated alumina, flame retardants and mattress bedding. It is also used as a rubber reinforcing agent, paper coating, filler, and in cosmetics. Aluminum trihydroxide is also used as an antacid and an antihyperphosphatemic (Lewis 1997).

Human Health – Tier 1

Carcinogenicity (C) Score (H, M or L): L
Aluminum trihydroxide was assigned a score of Low for carcinogenicity based on results from animal studies.

- Not classifiable as a human carcinogen (ACGIH 2008).
- Aluminum hydroxide was not carcinogenic after daily intraperitoneal administration to mice for 4 months at dosages up to 200 mg/kg/day (FAO/WHO 1989).

[7] A moiety is a discrete chemical entity that is a constituent part or component of a substance. A moiety of concern is often the parent substance itself for organic compounds. For inorganic compounds, the moiety of concern is typically a dissociated component of the substance or a transformation product.

- In a 6 month study in rats the effects of aluminum on renal function were and phosphate handling were studied. Rats (number/strain not reported) were given aluminum hydroxide (80 mg/kg, IP) 3 times/wk. No changes were observed in renal function and no evidence of carcinogenicity was found (Mahieu 1998).

Mutagenicity (M) and Genotoxicity Score (H, M or L): *L*
No mutagenicity and genotoxicity data were identified for aluminum hydroxide. A score of Low was assigned based on the U.S. EPA's assessment on flame retardants in printed circuit boards for aluminum hydroxide (U.S. EPA 2008).

- No relevant data on mutagenicity was identified for aluminum hydroxide.
- Aluminum hydroxide is estimated to be of low genotoxic potential (U.S. EPA 2008).

Reproductive (R) and Developmental (D) Toxicity Score (H, M or L): L
Aluminum trihydroxide was assigned a score of Low for reproductive and developmental toxicity based on negative results from animal studies.

- When high doses (≤ 1094 mg/kg/day) of aluminum hydroxide were orally administered to pregnant rats and mice during embryogenesis, no maternal or developmental toxicity occurred (Bingham 2001).
- No developmental effects occurred in Swiss mice (number not reported) at doses of 66.5, 133, or 266 mg/kg/day following gavage administration on gestation days 6-15 (Domingo 1989).
- No developmental toxicity occurred in Swiss albino CD-1 mice (number not reported) at a dose of 57.5 mg/kg/day following gavage administration on gestation days 6-15 (Colomina 1992).
- No developmental toxicity occurred in Sprague-Dawley rats (number not reported) at a gavage dose of 384 mg/kg/day on gestation days 6-15 (Gomez 1991).
- No developmental toxicity occurred in Wistar rats (number not reported) at gavage doses of 192, 384, and 768 mg/kg/day (Gomez 1990).

Endocrine Disruption (ED) Score (H, M or L): nd

- Aluminum trihydroxide is not listed as a potential endocrine disruptor on the EU Priority List of Suspected Endocrine Disruptors.
- Aluminum trihydroxide is not listed as a potential endocrine disruptor on the OSPAR List of Chemicals of Possible Concern.
- Aluminum trihydroxide is not listed as a potential endocrine disruptor on the Red List of Chemicals (CPA 2009).

Neurotoxicity (N) Score (H, M or L): M
Aluminum trihydroxide was assigned a score of Moderate for neurotoxicity based on results from animal studies and being present on the red list as a potential neurotoxicant.

- In a 30-day study rats (number/strain not reported) were fed aluminum in an oral diet with no significant effects noted and a reported NOAEL of 1252 mg/kg/day (ASTDR 2008).

- In a 90-day study rats (number/strain not reported) were given aluminum hydroxide with citric acid by oral gavage and demonstrated impaired learning in a labyrinth maze test. A LOAEL of 35 mg/kg/day was reported (ASTDR 2008).
- Aluminum hydroxide is expected to be of moderate hazard for neurotoxicity based on available data (U.S. EPA 2008).

Human Health – Tier 2

Acute Mammalian (AT) Toxicity Score (H, M or L): L
A score of Low for acute mammalian toxicity was assigned to aluminum trihydroxide based on an oral LD_{50} value greater than 5,000 mg/kg-bw. Data is from one route of exposure in two different species.

- *Oral*: TDL_0 (child) = 79,000 mg/kg (ChemIDplus 2010)
- *Oral*: TDL_0 (child) = 122,000 mg/kg (ChemIDplus 2010)
- *Oral*: LD_{50} (rat) > 5,000 mg/kg (ESIS 2000)

Corrosion/ Irritation (Skin/ Eye) (Cr) Score (H, M or L): M
Aluminum trihydroxide was assigned a score of Moderate for corrosion and irritation based on human studies and MSDS data.

- Aluminum trihydroxide may cause mild skin, eye and upper respiratory tract irritation (ScienceLab 2010).

Sensitization (Sn) Score (Skin and Respiratory) (H, M or L): L
Aluminum trihydroxide was assigned a score of Low for sensitization based on aluminum hydroxide testing negative for skin and respiratory sensitization.

- *Dermal*: Aluminum trihydroxide was not sensitizing. No other details were provided (ESIS 2000).
- *Respiratory/Dermal:* Aluminum trihydroxide was not sensitizing. No other details were provided (ESIS 2000).

Systemic/ Organ (ST) Toxicity Score (includes organ effects and immunotoxicity) (H, M or L): M
Aluminum trihydroxide was assigned a score of Moderate for systemic/organ toxicity based on potential immunotoxic effects in humans.

- The effects of dietary administration of aluminum hydroxide were examined in male Sprague-Dawley rats. Groups of 25 rats were fed a diet containing 14,470 ppm aluminum hydroxide or a control diet for 28 days. The mean daily aluminum dose was calculated as 302 mg/kg body weight/day. Dietary administration of aluminum hydroxide did not induce any signs of toxicity. Clinical observations during the 28-day treatment period and the recovery phase were similar in control and treated rats. There were no significant changes in hematology, clinical chemistry parameters, or organ weights (Hicks 1987).

- In a 6-week oral administration study in humans, a reduction in primed cytotoxic T-cells was observed and a LOAEL of 25 mg/kg/day was reported (ATSDR 2008).

Ecotoxicity

Acute Aquatic (AA) Toxicity Score (H, M or L): L
Aluminum trihydroxide was assigned a score of Low for acute aquatic toxicity based on LC_{50} values greater than 100 mg/L.

- 96-hour LC_{50} (*fish*) > 100 mg/L (ESIS 2000)
- 48-hour LC_{50} (*Daphnia magna*) > 100 mg/L (ESIS 2000)
- 72-hour EC_{50} (*Selenastrum capricornutum*) > 100 mg/L (ESIS 2000)

Chronic Aquatic (CA) Toxicity Score (H, M or L): *M*
No data was identified for aluminum trihydroxide. Aluminum trihydroxide was assigned a score of Moderate chronic aquatic toxicity based GHS criteria for chronic aquatic toxicity.

- There were no data identified on the chronic aquatic toxicity of aluminum hydroxide. The globally harmonized system (GHS) Categorization of poorly soluble substances for which no chronic or acute toxicity data exist are classified as chronic aquatic toxicity category 4, a "safety net" category. The Green Screen assigns these chemicals a rating of "moderate."

Environmental Fate

Persistence (P) Score (vH, H, M, or L): vH
Aluminum trihydroxide was assigned a score of very High for persistence based on the chemical being an inorganic compound and not having any identifiable biodegradation pathways at normal environmental conditions.

- As an oxidized inorganic compound, aluminum trihydroxide is not expected to biodegrade, oxidize further in air, or undergo hydrolysis at environmental conditions. No degradation process for aluminum trihydroxide could be identified at typical environmental conditions (US EPA 2008).

Bioaccumulation (B) Score (vH, H, M, or L): L
Aluminum trihydroxide was assigned a score of Low for bioaccumulation based on a BCF value less than 100.

- Aluminum hydroxide has a predicted BCF of 3.2 (U.S. EPA 2008).
- Aluminum hydroxide is not expected to be bioaccumulative (U.S. EPA 2008).

Physical Properties

Explosivity (Ex) Hazard Rating (H, M or L): L

Aluminum trihydroxide was assigned a Low for explosivity because no basis for concern was identified.

- Aluminum hydroxide is not explosive (ESIS 2000)

Flammability (F) Hazard Rating (H, M or L): L

Aluminum trihydroxide was assigned a Low for flammability because no basis for concern was identified.

- Aluminum hydroxide is not flammable (ESIS 2000)

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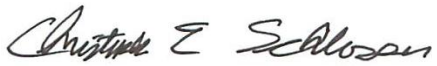
Aluminum trihydroxide Green Screen Evaluation Prepared By:



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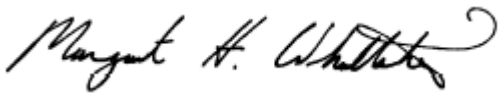

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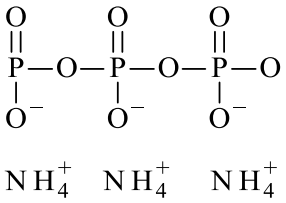
APPENDIX IX D: GREEN SCREEN FOR AMMONIUM POLYPHOSPHATE (CAS #68333-79-9)[8]

Also Called: AP 422, AP 462, APP (fireproofing agent), APP 422, Albaplas AP 95, Aluminum polyphosphate, Amgard CL, Amgard MC, Amgard TR, Ammonium ortho and polyphosphate solution, Ammonium orthophosphate, superphosphate, Ammonium polyphosphate, Ammonium polyphosphates, Antiblaze MC, Antiblaze MCM, Budit 3076, Budit 3076DC, Budit 3077, Budit 365, DFP-I, EINECS 269-789-9, EXO 462, Exolit 263, Exolit 422, Exolit 442, Exolit 454, Exolit 455, Exolit 462, Exolit 470, Exolit AP 422, Exolit AP 423, Exolit AP 462, FR-Cros 480, FR-Cros 484,Fire-Trol LCG-R, Flameguard PT 8, Hostaflam 423, Hostaflam AP 420, Hostaflam AP 422, Hostaflam AP 462, Hostaflam AP 464, Hostaflam TP-AP 751, Hostaflam TP-AP 752, Novawhite, Phos-Chek P 30, Phos-Chek P 40, Phos-Chek P 60, Poly-N 10-34-0, Poly-N 11-37-0, Polymetaphosphoric acid, ammonium salt, Polyphosphoric acid, ammonium salt, Sumisafe, Taien A, Taien H

Chemical Structure of Ammonium Polyphosphate:



***Note:** Data gaps for ammonium polyphosphate (CAS #6833-79-9) were addressed using the structurally similar chemical sodium tripolyphosphate (CAS #7758-29-4). The National Academy of Sciences selected sodium tripolyphosphate as a chemical surrogate for ammonium polyphosphate in the report "Toxicological Risks of Selected Flame-Retardant Chemicals (NAS 2000)."

For Polymers: Identify Monomers and Corresponding Properties

1. % of Each Monomer – n/a
2. Are the monomers blocked? – n/a
3. Molecular Weight (MW) of Polymer – ca 100,000 g/mol (Pinfa 2010).
4. % of Polymer with
   a) MW <500 – n/a
   b) MW <1,000 – n/a
5. % Weight Residual Monomers – n/a
6. Solubility/Dispersability/Swellability – ≤ 5 g/L (Clariant 2009)
7. Particle Size – approx. 15 µm (Clariant 1999)
8. Overall Polymer Charge – n/a

[8] CPA recommends independent third-party validation of all Green Screen assessments. No independent third-party validation has been done for this assessment . Companies may not make marketing claims based on a Green Screen assessment that has not undergone an independent validation.

Identify Applications/Functional Uses: Flame retardant

Green Screen Rating[9]: Ammonium polyphosphate was assigned a Green Screen Benchmark Score of 4 based on low human toxicity and ecotoxicity.

Green Screen (Version 1) Levels of Concern for Ammonium Polyphosphate														
Human – Tier 1					Human – Tier 2				Eco		Fate		Physical	
C	M	R/D	ED	N	AT	Cr	Sn	ST	AA	CA	P	B	Ex	F
L	L	*L*	nd	nd	L	L	L	*L*	L	*L*	L	L	L	L

*Endpoints in italics were assigned using estimated values and professional judgment (Structure Activity Relationships)

Transformation Products and Ratings:
Identify relevant fate and transformation products (i.e., dissociation products, transformation products, valence states) and/or moieties of concern[10]

Life Cycle Stage	Transformation Pathway	Transformation Products	CAS #	Green Screen Rating
End of Life	Water hydrolysis	Ammonium phosphate	7783-28-0 (USAN) and 10124-31-9	Not present on the Red List of chemicals (CPA 2009).
End of Life	Combustion	Ammonia	7664-41-7	Not present on the Red List of chemicals (CPA 2009).
End of Life	Combustion	Phosphorous oxides	1314-56-3 and 14452-66-5	Not present on the Red List of chemicals (CPA 2009).
End of Life	Combustion	Nitrogen oxides	10102-43-9	Not present on the Red List of chemicals (CPA 2009).

*The above transformation products were screened against the CPA's table of Red List chemicals; none were found.

[9] For inorganic chemicals with low human and ecotoxicity across all hazard endpoints and low bioaccumulation, persistence alone will not be deemed problematic. Inorganic chemicals that are only persistent will be evaluated under the criteria for Benchmark 4.

[10] A moiety is a discrete chemical entity that is a constituent part or component of a substance. A moiety of concern is often the parent substance itself for organic compounds. For inorganic compounds, the moiety of concern is typically a dissociated component of the substance or a transformation product.

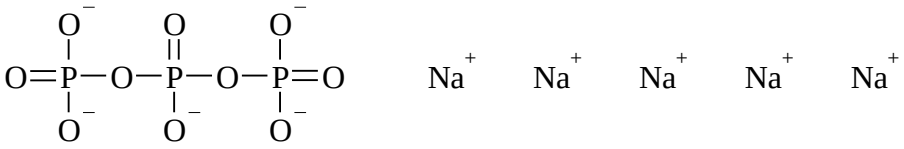
Introduction

Ammonium polyphosphate ("APP") is a solid, ionic, non-volatile polymer used for flame retardation (Clariant 2009). This white powder has a molecular weight of ca 100,000 g/mol and is almost completely insoluble in water and is completely insoluble in organic solvents (Pinfa 2010). The log K_{ow} is not applicable to APP because it is an inorganic salt and therefore will not partition between organic and aqueous phases (UNEP 2008). No PEL, STEL or TLV have been established for APP.

APP is an intumescent coating, meaning it swells as a result of heat exposure and produces a carbonaceous foam which is poor conductor of heat, thus retarding heat transfer (Clariant 1999). APP has excellent flame retardant characteristics in cellulose-containing materials such as paper and wood products but is also classified for use on steel and plastic surfaces as well as adhesives and sealants (Clariant 1999). APP is also used as a fertilizer (UNEP 2008).

Because there no relevant toxicity data were identified for the possible reproductive, developmental, acute and systemic toxicity of APP, a structurally similar surrogate was used. Sodium tripolyphosphate was selected as the chemical surrogate due to its structural similarity, use as a flame retardant, and use as a surrogate in several previous reports (NAS 2000).

Chemical Structure of Chemical Surrogate:



Sodium Tripolyphosphate (CAS #7758-29-4)

Human Health – Tier 1

Carcinogenicity (C) Score (H, M or L): L
APP was assigned a score of Low for carcinogenicity because no basis for concern was identified.

- APP is not listed as a known carcinogen by IARC, NTP, U.S. EPA, or CA Prop 65.

Mutagenicity (M) and Genotoxicity Score (H, M or L): L
APP was assigned a score of Low for mutagenicity and genotoxicity based on negative test results from several Ames assays.

- APP tested negative for mutagenicity in an Ames Test. No additional information provided (Pinfa 2010).
- In separate assays, APP (Exolit 422, technical quality) and Exolit 456 (90% APP and 10% melamine/formaldehyde) tested negative for mutagenicity in *Salmonella*

typhimurium tester strains TA 98, TA 100, TA 1535, TA 1537, and TA 1538, and *Escherichia coli* WP2uvrA with and without a metabolic activator at concentrations ranging from 4 to 5000 μg/plate in either a water or a DMSO vehicle (ESIS 2000).

Reproductive (R) and Developmental (D) Toxicity Score (H, M or L): *L*
Because no reproductive or developmental toxicity data were identified for APP, the structurally similar sodium tripolyphosphate was used as a surrogate. APP was assigned a score of Low based on analog data for sodium tripolyphosphate, which had no adverse effects on reproductive or developmental health.

Sodium tripolyphosphate

- Sodium tripolyphosphate had no effect on fertility, litter size, neonate growth, or neonate survival in a three generation reproduction study in rats administered 500 mg/kg-bw/day[11] sodium tripolyphosphate in their feed. No other details for this study were provided (NAS 2000).

Endocrine Disruption (ED) Score (H, M or L): nd

- APP is not listed as a potential endocrine disruptor on the EU Priority List of Suspected Endocrine Disruptors.
- APP is not listed as a potential endocrine disruptor on the OSPAR List of Chemicals of Possible Concern.
- APP is not listed as a potential endocrine disruptor on the Red List of Chemicals (CPA 2009).

Neurotoxicity (N) Score (H, M or L): nd

- APP is not classified as a developmental neurotoxicant (Grandjean and Landrigan 2006).
- APP is not listed as a potential neurotoxicant on the Red List of Chemicals (CPA 2009).

Human Health – Tier 2

Acute Mammalian (AT) Toxicity Score (H, M or L): L
APP was assigned a score of Low for acute mammalian toxicity based on oral and dermal LD_{50} values greater than 2,000 mg/kg-bw. Data was from three different routes in two different species.

- *Oral*: An LD_{50} of > 2,000 mg/kg-bw was identified in the rat (UNEP 2008).
- *Oral*: An LD_{50} of 4,740 mg/kg-bw was identified in the rat (Clariant 2009).
- *Oral*: An LD_{50} of > 2,000 mg/kg-bw was identified in the rabbit (UNEP 2008).
- *Inhalation*: An LC_{50} of > 5.09 mg/L (4-hr exposure) was identified in the rat (UNEP 2008).

[11] The original report by Hodge (1964a) provides a concentration of 0.5% sodium tripolyphosphate administered to rats. The conversion to mg/kg-bw/day is as follows (assuming use of Fisher rat, as the strain is not provided in the study):
(5,000 mg sodium tripolyphosphate/kg chow * 0.018 kg chow/day)/0.180 kg-bw = 500 mg/kg-bw/day

- *Dermal*: An LD_{50} of >5,000 mg/kg-bw was identified in the rat (UNEP 2008).
- *Dermal*: An LD_{50} of >2,000 mg/kg-bw was identified in the rat (UNEP 2008).

Corrosion/ Irritation (Skin/ Eye) (Cr) Score (H, M or L): L

APP was assigned a score of Low for corrosion and irritation based on animal studies that showed the chemical to not be irritating to the skin or eyes of rabbits.

- *Dermal*: APP was not irritating to the skin of rabbits following a 4-hour occlusion in a Draize test. The test substance was 70% ammonium polyphosphate and 30% monoammonium phosphate. Additional details concerning this study were not provided (UNEP 2008).
- *Dermal*: APP was slightly irritating to the skin of rabbits following a 24-hour occlusive Patch test. Additional details concerning this study were not provided (ESIS 2000).
- *Dermal*: Exolit 456 (90% APP and 10% monoammonium phosphate) was not irritating in an OECD 404 "Acute Dermal irritation/corrosion" test. Additional details concerning this study were not provided (ESIS 2000).
- *Ocular*: APP was not irritating to the eyes of rabbits in a Draize test. The test substance was 70% ammonium polyphosphate and 30% monoammonium phosphate. Additional details concerning this study were not provided (ESIS 2000).
- *Ocular*: APP was not irritating to the eyes of rabbits. Additional details concerning this study were not provided (ESIS 2000).
- Ocular: Exolit 456 (90% APP and 10% melamine/formaldehyde) was not irritating to the eyes of rabbits following an OECD 405 "Acute Eye Irritation/Corrosion" test. Additional details concerning this study were not available (ESIS 2000).

Sensitization (Sn) Score (Skin and Respiratory) (H, M or L): L

APP was assigned a score of Low for sensitization because animal tests showed the chemical to be a poor sensitizing agent.

- *Dermal*: APP was found to be a poor skin-sensitizing agent in the Magnusson and Kligman maximization test. Twenty female guinea pigs were initially injected intradermally with a 25% (w/v) solution of APP. Topical induction was then attempted on day 7 with filter paper patches containing 75% (w/w) APP in distilled water. Only 1 of 20 animals had skin changes (scattered mild redness) at the application site 1 hour after removal of the patches. No animals had any visible skin reactions 24 hours after patch removal. None of the animals showed any tissue reaction either 24 or 48 hours after topical challenge with filter paper patches containing 50% or 75% solutions of APP. No other data was provided for this study (Safepharm 1993).

Systemic/ Organ (ST) Toxicity Score (includes organ effects and immunotoxicity) (H, M or L): *L*

Because no relevant systemic/organ toxicity data were identified for APP, the structurally similar sodium tripolyphosphate was used as a surrogate. APP was assigned a score of Low for systemic/organ toxicity based on analog data.

Sodium tripolyphosphate:

- Male and female rats (36/sex/dose) were administered 0, 3, and 5% sodium tripolyphosphate in their diets for 24 weeks. Nephrocalcinosis was observed at 3% dose level only. No other information was provided (JECFA 1974).

Ecotoxicity

Acute Aquatic (AA) Toxicity Score (H, M or L): L

APP was assigned a score of Low for acute aquatic toxicity based on LC_{50} values of 100 mg/L or greater.

- APP has an LC_{50} of > 101 mg/L in *Oncorhynchus mykiss* (freshwater fish, 96 hour) (UNEP 2008).
- APP has an LC_{50} of 100 - 1,000 mg/L in *Danio rerio* (freshwater fish, 96 hour) (Clariant 2009).

Chronic Aquatic (CA) Toxicity Score (H, M or L): *L*

APP was assigned a Low for chronic aquatic toxicity based on professional opinion.

- APP has a molecular weight of 100,000 g/mol (Pinfa 2010). Insoluble polymers are not expected to be toxic to aquatic organisms unless the material is in the form of finely divided particles. Toxicity of these polymer particles does not depend on a specific structural feature, but occurs from occlusion of respiratory organs such as gills. For these polymers, toxicity occurs at high concentrations; >100 mg/L for acute toxicity and >10 mg/L for chronic toxicity (U.S. EPA 2010).

Environmental Fate

Persistence (P) Score (vH, H, M, or L): L

APP was assigned a score of Low for persistence based on a soil half-life less than 30 days and rapid biodegradation.

- APP breaks down into ammonia and phosphate rapidly in soil and sewage sludge (Leisewitz 2000).
- Hydrolysis of APP occurs very slowly in neutral solutions (UNEP 2008).
- The half-life of APP in soil ranged from 1.6 to 2.0 days under anaerobic conditions and from 5.3 to 8.7 days under aerobic conditions (UNEP 2008).
- Biodegradation tests are not applicable to APP because the methods are based on carbon oxidation and the ammonium present in APP may be nitrified (UNEP 2008).

Bioaccumulation (B) Score (vH, H, M, or L): L

APP was assigned a score of Low for bioaccumulation based on its insolubility.

- APP is not expected to bioaccumulate because it is an inorganic polymer (avg. MW = 100,000) and therefore insoluble in water (Pinfa 2010).

Physical Properties

Explosivity (Ex) Hazard Rating (H, M or L): L

APP was assigned a score of Low for explosivity because no basis for concern was identified.

- APP is not explosive- no other data provided (Clariant 2009).

Flammability (F) Hazard Rating (H, M or L): L

APP was assigned a score of Low for flammability because no basis for concern was identified.

- APP is not flammable- no other data provided (Clariant 2009).

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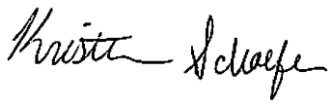
Ammonium Polyphosphate Green Screen Evaluation Prepared By:



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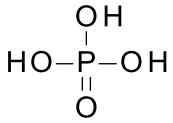
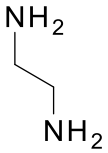
APPENDIX IX E: GREEN SCREEN FOR ETHYLENEDIAMINE PHOSPHATE (CAS #14582-17-6)[12]

Also Called: 1,2-Ethanediamine, phosphate, Ethylenediamine, salt with phosphoric acid

Chemical Structure of Ethylenediamine Phosphate:





***Note:** Data gaps for ethylene phosphate (CAS #14852-17-6) were addressed using the individual components of this mixture, ethylenediamine (CAS #107-15-3) and phosphoric acid (CAS #7664-38-2) as chemical surrogates.

For Inorganic Chemicals:
Define Form & Physiochemical Properties

4. Particle size (e.g. silica of respirable size) – n/a
5. Structure (e.g. amorphous vs. crystalline) – n/a
6. Mobility (e.g. Water solubility, volatility) – n/a

Identify Applications/Functional Uses: Flame retardant

Green Screen Rating[13]: Ethylenediamine phosphate was assigned a Green Screen Benchmark Score of 2 based on High chronic aquatic toxicity (CA), Moderate mutagenicity (M) and reproductive and developmental toxicity (R/D) (2d).

Green Screen (Version 1.0) Levels of Concern for Ethylenediamine Phosphate														
Human – Tier 1					Human – Tier 2				Eco		Fate		Physical	
C	M	R/D	ED	N	AT	Cr	Sn	ST	AA	CA	P	B	Ex	F
L	*M*	*M*	nd	nd	*M*	*H*	*H*	*M*	L	H	M	L	L	L

*Endpoints in italics were assigned using estimated values and professional judgment (Structure Activity Relationships).

[12] CPA recommends independent third-party validation of all Green Screen assessments. No independent third-party validation has been done for this assessment . Companies may not make marketing claims based on a Green Screen assessment that has not undergone an independent validation.

[13] For inorganic chemicals with low human and ecotoxicity across all hazard endpoints and low bioaccumulation, persistence alone will not be deemed problematic. Inorganic chemicals that are only persistent will be evaluated under the criteria for Benchmark 4.

Transformation Products and Ratings:
Identify relevant fate and transformation products (i.e., dissociation products, transformation products, valence states) **and/or moieties of concern**[14]

Life Cycle Stage	Transformation Pathway	Transformation Products	CAS #	Green Screen Rating
End of life	Dissociation	Ethylenediamine	107-15-3	Present on the Red List of chemicals (CPA 2009).
End of life	Dissociation	Phosphoric acid	7664-38-2	Not present on the Red List of chemicals (CPA 2009).
End of life	Combustion	Carbon oxides	630-08-0 and 124-38-9	Present on the Red List of chemicals (CPA 2009).
End of Life	Combustion	Phosphorous oxides	1314-56-3 and 14452-66-5	Not present on the Red List of chemicals (CPA 2009).
End of Life	Combustion	Nitrogen oxides	10102-43-9	Not present on the Red List of chemicals (CPA 2009).

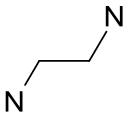
*The above transformation products were screened against the CPA's table of Red List chemicals.

Introduction

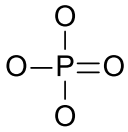
Ethylenediamine phosphate (CAS #14852-17-6) is a non-halogenated flame retardant composed of a mixture of ethylenediamine and phosphoric acid. No PEL, STEL or TLV have been established for ethylenediamine phosphate. Because there no relevant toxicity data were identified to assess possible skin/eye corrosion, skin/respiratory sensitization, mutagenicity, reproductive, developmental, acute or systemic toxicity of ethylenediamine phosphate, individual components of EDP were evaluated to address datagaps: ethylenediamine (CAS #107-15-3) and phosphoric acid (CAS #7664-38-2).

[14] A moiety is a discrete chemical entity that is a constituent part or component of a substance. A moiety of concern is often the parent substance itself for organic compounds. For inorganic compounds, the moiety of concern is typically a dissociated component of the substance or a transformation product.

Chemical Structure of Surrogates:



Ethylenediamine (CAS #107-15-3)



Phosphoric acid (CAS #7664-38-2)

Human Health – Tier 1

Carcinogenicity (C) Score (H, M or L): L

Ethylenediamine phosphate was assigned a score of Low for carcinogenicity because no basis for concern was identified.

- Ethylenediamine phosphate is not listed as a known carcinogen by IARC, NTP, U.S. EPA, or CA Prop 65.

Mutagenicity (M) and Genotoxicity Score (H, M or L): *M*

Because no mutagenicity and genotoxicity data were identified for ethylenediamine phosphate, the components of the mixture were used as a surrogate. Ethylenediamine phosphate was assigned a score of Moderate for mutagenicity and genotoxicity based on conflicting results from several genotoxicity studies.

Ethylenediamine

- *In vitro* - An Ames Reverse Mutation assay was performed using *Salmonella typhimurium* tester strains TA100 and TA1535 in the presence and absence of metabolic activation at concentrations ranging from 0-6667 µg/plate and determined to be positive for mutagenicity (UNEP 2001).
- *In vitro* - An Ames Reverse Mutation assay was performed using *Salmonella typhimurium* tester strains TA98 and TA1537 in the presence and absence of metabolic activation at concentrations ranging from 0-3333 µg/plate and determined to be negative for mutagenicity (UNEP 2001).
- *In vitro* - An Ames Reverse Mutation assay was performed using *Salmonella typhimurium* tester strains TA98, TA100, TA 1535, TA 1537 and TA1538 in the presence and absence of metabolic activation at concentrations ranging from 90-9000 µg/plate and determined to be negative for mutagenicity (UNEP 2001).
- *In vitro* - An Ames Reverse Mutation assay was performed using *Salmonella typhimurium* tester strains TA98, TA100, TA 1535, and TA 1537 in the presence and absence of metabolic activation at concentrations ranging from 0-5000 µg/plate. Mutagenicity was ambiguous in TA 100 with metabolic activation, and negative in all other strains (UNEP 2001).
- *In vitro* – An HGPRT assay was performed using Chinese hamster ovary cells in the presence and absence of metabolic activation at concentrations ranging from 0-897 µg/plate and found to be negative for mutagenicity (UNEP 2001).
- *In vitro* – A sister chromatid exchange assay was performed using Chinese hamster ovary cells in the presence and absence of metabolic activation at concentrations ranging from 0-448 µg/plate and found to be negative for mutagenicity (UNEP 2001).

Phosphoric acid

- *In vitro* - An Ames Reverse Mutation assay was performed using *Salmonella typhimurium* tester strains TA97, TA98, TA100, and TA104 in the presence and absence of metabolic activation at concentrations ranging from 917-3668 µg/plate and determined to be negative for mutagenicity (CCRIS 2010).
- *In vitro* - An Ames Reverse Mutation assay was performed using *Salmonella typhimurium* tester strains in the presence and absence of metabolic activation and determined to be negative for mutagenicity. Strains and concentrations were not reported (ESIS 2000).

Reproductive (R) and Developmental (D) Toxicity Score (H, M or L): *M*

Because no reproductive and developmental toxicity data were identified for ethylenediamine phosphate, the components of the mixture were used as a surrogate. Ethylenediamine phosphate was assigned a score of Moderate for reproductive and developmental toxicity based on animal studies for ethylenediamine.

Ethylenediamine

- A 2-generation reproductive study was conducted on F344 rats (13 male and 26 female/dose level). Ethylenediamine was administered at concentrations of 50, 150, and 500 mg/kg by oral feeding daily starting 100 days prior to mating of F_0 until weaning of F_2 rats. Significant reduction in parental body weight gain was observed in the 150 and 500 mg/kg groups of male and female rats. A higher incidence of hepatocellular pleomorphism in both sexes of the 500 mg/kg group was observed and a significant decrease in the prevalence of kidney tubular mineralization in female rats at 150 mg/kg. No evidence of fertility impairment or embryotoxic effects was observed. A parental NOAEL of 50 mg/kg and a F_1 offspring NOAEL of 150 mg/kg were reported by the authors (UNEP 2001).
- A development toxicity study was performed on New Zealand White rabbits (26/dose). Rabbits were administered 0, 10, 40, and 80 mg/kg of ethylenediamine (purity not reported) on gestation days six through nineteen. No significant effects were observed on maternal food intake, body weight gain, liver or kidney weight, or uterine weight. No effects were observed on viability, litter size, fetal weight or fetal morphology. A NOAEL of > 80 mg/kg for maternal and fetal toxicity was reported by the authors (UNEP 2001).

Phosphoric acid

- A 1-generation reproductive study was conducted on rats (strain/sex/number not reported). Phosphoric acid was administered at concentrations of 180 and 375 mg/kg by oral feeding for 29 weeks. No harmful effects on the growth of the offspring or parental rats were reported at the highest concentration (ESIS 2000).

Endocrine Disruption (ED) Score (H, M or L): nd

- Ethylenediamine phosphate is not listed as a potential endocrine disruptor on the EU Priority List of Suspected Endocrine Disruptors.
- Ethylenediamine phosphate is not listed as a potential endocrine disruptor on the OSPAR List of Chemicals of Possible Concern.
- Ethylenediamine phosphate is not listed as a potential endocrine disruptor on the Red List of Chemicals (CPA 2009).

Neurotoxicity (N) Score (H, M or L): nd

- Ethylenediamine phosphate is not classified as a developmental neurotoxicant (Grandjean and Landrigan 2006).
- Ethylenediamine phosphate is not listed as a potential neurotoxicant on the Red List of Chemicals (CPA 2009).

Human Health – Tier 2

Acute Mammalian (AT) Toxicity Score (H, M or L): *M*

Because no acute mammalian toxicity data were identified for ethylenediamine phosphate, the components of the mixture were used as a surrogate. A score of Moderate for acute mammalian toxicity was assigned to ehtylenediamine phosphate based on oral LD_{50} values between 50 and 2,000 mg/kg-bw and dermal LD_{50} values between 200 and 2,000 mg/kg-bw. Data is from two surrogates using three different routes in three different species.

Ethylenediamine

- *Oral*: LD_{50} (rat) = 637 mg/kg (UNEP 2001).
- *Oral*: LD_{50} (rat) = 1850 mg/kg (UNEP 2001).
- *Oral*: LD_{50} (rat) = 1050 mg/kg (UNEP 2001).
- *Oral*: LD_{50} (rat) = 1500 mg/kg (UNEP 2001).
- *Oral*: LD_{50} (mouse) = 1000 mg/kg (ChemIDPlus 2010).
- *Dermal*: LD_{50} (rabbit) = 560 mg/kg (UNEP 2001).
- *Dermal*: LD_{50} (rat) = 1000 mg/kg (UNEP 2001).
- *Inhalation*: LC_{50} (rat) = 29 mg/L (ChemIDPlus 2010).

Phosphoric acid

- *Oral*: LD_{50} (rat) = 1530 mg/kg (ESIS 2000).
- *Dermal*: LD_{50} (rabbit) = 2740 mg/kg (ESIS 2000).
- *Inhalation*: LC_{50} (rabbit) = 1.689 mg/L (ESIS 2000).

Corrosion/ Irritation (Skin/ Eye) (Cr) Score (H, M or L): *H*

Because no corrosion/irritation toxicity data were identified for ethylenediamine phosphate, the components of the mixture were used as a surrogate. Ethylenediamine phosphate was assigned a score of High for corrosion and irritation based on animal studies showing the chemical to be corrosive and irritating.

Ethylenediamine

- *Dermal*: Application of an aqueous solution of 70% ethylenediamine to the skin of rabbits (# not reported) caused complete destruction within 6 to 12 minutes. A 10% solution of ethylenediamine in water caused a burn within 24 hours. A dermal NOEL of 0.1% was reported by the authors (UNEP 2001).
- *Ocular*: A 10% solution in water caused moderate corneal damage and extensive conjunctivitis. A 1% solution was essentially non-irritating. Species and number of animals tested were not reported (UNEP 2001).
- *Ocular*: Vapors ethylenediamine are mildly irritating to the eye after 10 seconds at 200 ppm while 400 ppm is intolerable. Species and number of test subjects were not reported (UNEP 2001).

Phosphoric acid

- *Dermal:* Several dermal studies have been completed on the compound. Phosphoric has been classified has irritating and corrosive at concentrations ranging from 35 to 100% (ESIS 2000)
- *Ocular:* Phosphoric acid was found to be not irritating to the eyes of rabbits following OECD guideline 405 at concentrations of 10 and 17% phosphoric acid (ESIS 2000).
- *Ocular:* Phosphoric acid is classified as potentially irritating to the eyes of humans (ESIS 2000).

Sensitization (Sn) Score (Skin and Respiratory) (H, M or L): *H*

Because no sensitization data were identified for ethylenediamine phosphate, the components of the mixture were used as a surrogate. Ethylenediamine phosphate was assigned a score of High for sensitization based on ethylenediamine testing positive for skin sensitization.

Ethylenediamine

- *Dermal*: Several skin sensitization studies have been reported for ethylenediamine including the following: guinea pig maximization test, draize test, repeated insult patch test, single injection adjuvant test, mouse optimization test, and a mouse ear swelling test. The test substance was confirmed to be sensitizing in the reported studies (UNEP 2001).
- *Respiratory/Dermal:* Ethylenediamine is associated with risk phrase 42/43. May cause sensitization by inhalation and skin contact (EINECS 2010).

Phosphoric acid

- *Dermal:* Phosphoric acid is classified as not sensitizing to humans. No other data was available for this study (ESIS 2000).

Systemic/ Organ (ST) Toxicity Score (includes organ effects and immunotoxicity) (H, M or L): *M*

Because no systemic/organ toxicity data were identified for ethylenediamine phosphate, the components of the mixture were used as a surrogate. Ethylenediamine phosphate was assigned a score of Moderate for systemic/organ toxicity based on repeat-dose analog studies suggesting renal toxicity in rodents.

Ethylenediamine

- A 13 week repeat dose oral toxicity study was conducted on F344 rats (10/sex/group). Concentrations of 0, 100, 200, 400, 600, and 800 mg/kg of ethylenediamine (purity not reported) were administered daily (5 days/week) by oral gavage for 13 weeks. Body weight gains were decreased in male and female rats administered 200 to 800 mg/kg. Several females in the 600 mg/kg and higher groups appeared to have smaller uterine horns and the 800 mg/kg group had smaller ovaries. Renal tubular lesions were noted in the 600 and 800 mg/kg groups. Male and female rats also exhibited bilateral cataracts in the 600 mg/kg group after 12 weeks. A LOAEL of 100 mg/kg was reported by the authors. This test study was reported to have followed OECD guideline 408 "Subchronic Oral Toxicity – Rodent: 90-day Study" (UNEP 2001).
- A 13 week repeat dose oral toxicity study was conducted on B6C3F1 mice (10/sex/group). Concentrations of 0, 25, 50, 100, 200, and 400 mg/kg of

ethylenediamine (purity not reported) were administered daily (5 days/week) by oral gavage for 13 weeks. No body weight changes were observed. There were no treatment related gross lesions. Histopathologic changes were noted in the kidneys at 499 mg/kg. The kidney lesion was characterized by mild to moderate degeneration of the renal tubular epithelium. A NOEL of 200 mg/kg was reported by the authors. This test study was reported to have followed OECD guideline 408 "Subchronic Oral Toxicity – Rodent: 90-day Study" (UNEP 2001).

Phosphoric acid

- No relevant data were identified for this phosphoric acid.

Ecotoxicity

Acute Aquatic (AA) Toxicity Score (H, M or L): L

Ethylenediamine phosphate was assigned a score of Low for acute aquatic toxicity based on LC_{50} values greater than 100 mg/L.

- An LC_{50} of > 100 mg/L was identified in fish (fish, 96 hour) (Fisk et al. 2003).
- ECOSAR – Ethylenediamine phosphate is designated to the aliphatic amines and neutral organics ECOSAR classes. The estimated L/EC_{50} values are 6266.691 mg/L (daphnid, 48 hr), and 320.865 mg/L (algae, 96 hr) (U.S. EPA 2009).

Chronic Aquatic (CA) Toxicity Score (H, M or L): H

Ethylenediamine phosphate was assigned a score of High for chronic aquatic toxicity based on an NOEC value < 0.1 mg/L.

- ECOSAR – The estimated ChV values are 2375.747 mg/L (fish, 96 hr), 0.082 mg/L (daphnid, 48 hr), and 723.378 mg/L (algae, 96 hr) (U.S. EPA 2009).

Environmental Fate

Persistence (P) Score (vH, H, M, or L): M

Ehtylenediamine phosphate was assigned a score of Moderate for persistence based on a soil half life of 30 days and water half life of 15 days.

- EPI Suite – BIOWIN model results indicate ethylenediamine phosphate is not readily biodegrade, and has a predicted degradation time of weeks. STP removal expected using BIOWIN/EPA Draft Method results indicate 75.06% total removal, with 74.44% due to biodegradation. Fugacity III modeling predicts 67.1% partitioning to soil with a half-life of 30 days, and 32.9% partitioning to water with a half-life of 15 days (U.S. EPA 2010).

Bioaccumulation (B) Score (vH, H, M, or L): L

Ethylenediamine phosphate was assigned a score of Low for bioaccumulation based on a BCF value less than 100.

- BCFBAF predicts a bioconcentration factor (BCF) of 3.162 L/kg wet-wt and a log K_{ow} of -4.54 (U.S. EPA 2010). BCF is used in instances where log Kow is <5.

Physical Properties

Explosivity (Ex) Hazard Rating (H, M or L): L

Because no explosivity data were identified for ethylenediamine phosphate, the components of the mixture were used as a surrogate. Ethylenediamine phosphate was assigned a score of Low for explosivity because no basis for concern was identified.

Ethylenediamine

- Ethylenediamine is stable (ScienceLab 2008).

Phosphoric acid

- Phosphoric acid is not explosive (ESIS 2000).

Flammability (F) Hazard Rating (H, M or L): L

Because no flammability data were identified for ethylenediamine phosphate, the components of the mixture were used as a surrogate. Ethylenediamine phosphate was assigned a score of Low for explosivity because no basis for concern was identified.

Ethylenediamine

- Ethylenediamine is flammable (ScienceLab 2008).

Phosphoric acid

- Phosphoric acid is not flammable (ESIS 2000).

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EPI Suite Results for Ethylenediamine Phosphate:

CAS Number: 14852-17-6
SMILES : NCCN(H)(H)(H)OP(=O)(O)O
CHEM : 1,2-Ethanediamine, phosphate
MOL FOR: C2 H11 N2 O4 P1
MOL WT : 158.10
---------- EPI SUMMARY (v4.00) ----------

Physical Property Inputs:
Log Kow (octanol-water): ------
Boiling Point (deg C) : ------
Melting Point (deg C) : ------
Vapor Pressure (mm Hg) : ------
Water Solubility (mg/L): ------
Henry LC (atm-m3/mole) : ------

Log Octanol-Water Partition Coef (SRC):
Log Kow (KOWWIN v1.67 estimate) = -4.54

Boiling Pt, Melting Pt, Vapor Pressure Estimations (MPBPVP v1.43):
Boiling Pt (deg C): 480.00 (Adapted Stein & Brown method)
Melting Pt (deg C): 90.27 (Mean or Weighted MP)
VP(mm Hg,25 deg C): 6.06E-011 (Modified Grain method)
VP (Pa, 25 deg C) : 8.07E-009 (Modified Grain method)
Subcooled liquid VP: 2.58E-010 mm Hg (25 deg C, Mod-Grain method)
: 3.44E-008 Pa (25 deg C, Mod-Grain method)

Water Solubility Estimate from Log Kow (WSKOW v1.41):
Water Solubility at 25 deg C (mg/L): 1e+006
log Kow used: -4.54 (estimated)
no-melting pt equation used

Water Sol Estimate from Fragments:
Wat Sol (v1.01 est) = 1e+006 mg/L

ECOSAR Class Program (ECOSAR v1.00):
Class(es) found:
Aliphatic Amines

Henrys Law Constant (25 deg C) [HENRYWIN v3.20]:
Bond Method : 9.03E-027 atm-m3/mole (9.15E-022 Pa-m3/mole)
Group Method: Incomplete
For Henry LC Comparison Purposes:
User-Entered Henry LC: not entered
Henrys LC [via VP/WSol estimate using User-Entered or Estimated values]:
HLC: 1.261E-017 atm-m3/mole (1.277E-012 Pa-m3/mole)
VP: 6.06E-011 mm Hg (source: MPBPVP)
WS: 1E+006 mg/L (source: WSKOWWIN)

Log Octanol-Air Partition Coefficient (25 deg C) [KOAWIN v1.10]:
Log Kow used: -4.54 (KowWin est)
Log Kaw used: -24.433 (HenryWin est)
Log Koa (KOAWIN v1.10 estimate): 19.893
Log Koa (experimental database): None

Probability of Rapid Biodegradation (BIOWIN v4.10):
Biowin1 (Linear Model) : 0.8261
Biowin2 (Non-Linear Model) : 0.8669
Expert Survey Biodegradation Results:
Biowin3 (Ultimate Survey Model): 2.8742 (weeks)
Biowin4 (Primary Survey Model) : 3.6629 (days-weeks)
MITI Biodegradation Probability:
Biowin5 (MITI Linear Model) : 0.3647
Biowin6 (MITI Non-Linear Model): 0.2299
Anaerobic Biodegradation Probability:
Biowin7 (Anaerobic Linear Model): 0.6277
Ready Biodegradability Prediction: NO

Hydrocarbon Biodegradation (BioHCwin v1.01):
Structure incompatible with current estimation method!

Sorption to aerosols (25 Dec C)[AEROWIN v1.00]:
Vapor pressure (liquid/subcooled): 3.44E-008 Pa (2.58E-010 mm Hg)
Log Koa (Koawin est): 19.893
Kp (particle/gas partition coef. (m3/ug)):
Mackay model : 87.2
Octanol/air (Koa) model: 1.92E+007
Fraction sorbed to airborne particulates (phi):
Junge-Pankow model : 1
Mackay model : 1
Octanol/air (Koa) model: 1

Atmospheric Oxidation (25 deg C) [AopWin v1.92]:
Hydroxyl Radicals Reaction:
OVERALL OH Rate Constant = 42.6481 E-12 cm3/molecule-sec
Half-Life = 0.251 Days (12-hr day; 1.5E6 OH/cm3)
Half-Life = 3.010 Hrs
Ozone Reaction:
No Ozone Reaction Estimation
Fraction sorbed to airborne particulates (phi):
1 (Junge-Pankow, Mackay avg)
1 (Koa method)
Note: the sorbed fraction may be resistant to atmospheric oxidation

Soil Adsorption Coefficient (KOCWIN v2.00):
Koc : 6.269 L/kg (MCI method)
Log Koc: 0.797 (MCI method)
Koc : 0.02976 L/kg (Kow method)
Log Koc: -1.526 (Kow method)

Aqueous Base/Acid-Catalyzed Hydrolysis (25 deg C) [HYDROWIN v2.00]:
Rate constants can NOT be estimated for this structure!

Bioaccumulation Estimates (BCFBAF v3.00):
Log BCF from regression-based method = 0.500 (BCF = 3.162 L/kg wet-wt)
Log Biotransformation Half-life (HL) = -2.8838 days (HL = 0.001307 days)
Log BCF Arnot-Gobas method (upper trophic) = -0.049 (BCF = 0.893)
Log BAF Arnot-Gobas method (upper trophic) = -0.049 (BAF = 0.893)
Kow log used: -4.54 (estimated)

Volatilization from Water:

Henry LC: 9.03E-027 atm-m3/mole (estimated by Bond SAR Method)
Half-Life from Model River: 8.153E+022 hours (3.397E+021 days)
Half-Life from Model Lake : 8.894E+023 hours (3.706E+022 days)

Removal In Wastewater Treatment:
Total removal: 1.85 percent
Total biodegradation: 0.09 percent
Total sludge adsorption: 1.75 percent
Total to Air: 0.00 percent
(using 10000 hr Bio P,A,S)

Removal In Wastewater Treatment:
Total removal: 75.06 percent
Total biodegradation: 74.44 percent
Total sludge adsorption: 0.62 percent
Total to Air: 0.00 percent
(using Biowin/EPA draft method)

Level III Fugacity Model:

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	6.65e-016	6.02	1000
Water	32.9	360	1000
Soil	67.1	720	1000
Sediment	0.0688	3.24e+003	0

Persistence Time: 622 hr

ECOSAR Results for Ethylenediamine Phosphate:

SMILES : NCCN(H)(H)(H)OP(=O)(O)O
CHEM : 1,2-Ethanediamine, phosphate
CAS Num: 014852-17-6
ChemID1:
ChemID2:
ChemID3:
MOL FOR: C2 H11 N2 O4 P1
MOL WT : 158.10
Log Kow: -4.54 (KowWin estimate)
Melt Pt:
Wat Sol: 1E+006 mg/L (WskowWin estimate)

ECOSAR v1.00 Class(es) Found

Aliphatic Amines

ECOSAR Class	Organism	Duration	End Pt	Predicted mg/L (ppm)
Aliphatic Amines	: Fish	96-hr	LC50	2.4e+005
Aliphatic Amines	: Daphnid	48-hr	LC50	6266.691
Aliphatic Amines	: Green Algae	96-hr	EC50	320.865
Aliphatic Amines	: Fish		ChV	2375.747
Aliphatic Amines	: Daphnid		ChV	0.082
Aliphatic Amines	: Green Algae		ChV	723.378
Aliphatic Amines	: Fish (SW)	96-hr	LC50	2.42e+005
Aliphatic Amines	: Mysid Shrimp (SW)	96-hr	LC50	6979.869
Aliphatic Amines	: Green Algae (SW)	96-hr	EC50	322.587

Aliphatic Amines : Fish (SW) ChV 2375.747
Aliphatic Amines : Mysid Shrimp (SW) ChV 0.082
Aliphatic Amines : Green Algae (SW) ChV 564.342

Neutral Organic SAR	: Fish	96-hr	LC50	4.2e+007 *
(Baseline Toxicity)	: Daphnid	48-hr	LC50	1.1e+007 *
	: Green Algae	96-hr	EC50	3.23e+005
	: Fish		ChV	4.6e+006 *
	: Daphnid		ChV	3.19e+005
	: Green Algae		ChV	35379.375

Note: * = asterisk designates: Chemical may not be soluble enough to measure this predicted effect.

Aliphatic Amines:

For Fish 96-hr LC50: For aliphatic amines with log Kow greater than 7.0, a test duration of greater than 96 hrs may be required for proper expression of toxicity. Also, if the toxicity value obtained by the use of this equation exceeds the water solubility (measured or estimated), mortalities greater than 50% would not be expected in a saturated solution during an exposure period of 96 hrs.

For Daphnid 48-hr LC50: For aliphatic amines with log Kow greater than 5.0, a test duration of greater than 48 hrs may be required for proper expression of toxicity. Also, if the toxicity value obtained by the use of this equation exceeds the water solubility (measured or estimated), significant mortalities would not be expected in a saturated solution during an exposure period of 48 hrs.

For Green Algae Acute Toxicity Values: If the log Kow of the chemical is greater than 7, or if the compound is solid and the EC50 exceeds the water solubility by 10X, no effects at saturation are predicted for these endpoints.

For Mysid Shrimp Acute Toxicity Values: If the log Kow of the chemical is greater than 6, or if the compound is solid and the EC50 exceeds the water solubility by 10X, no effects at saturation are predicted for these endpoints.

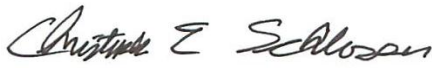
For Fish and Daphnid Chronic Toxicity Values: If the log Kow of the chemical is greater than 8.0, or if the compound is solid and the ChV exceeds the water solubility by 10X, no effects at saturation are predicted for these endpoints.

For Green Algae Chronic Toxicity Values: If the log Kow of the chemical is greater than 7.0, or if the compound is solid and the ChV exceeds the water solubility by 10X, no effects at saturation are predicted for these endpoints.

ECOSAR v1.00 SAR Limitations:

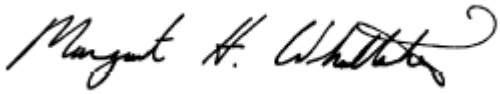
Maximum LogKow: 6.0 (Fish, Mysid LC50)
Maximum LogKow: 5.0 (Daphnid LC50)
Maximum LogKow: 7.0 (Green Algae EC50)
Maximum LogKow: 8.0 (Fish, Daphnid ChV)
Maximum LogKow: 7.0 (Green Algae ChV)
Maximum Mol Wt: 1000
Baseline Toxicity SAR Limitations:----------
Maximum LogKow: 5.0 (Fish 96-hr LC50; Daphnid LC50)
Maximum LogKow: 6.4 (Green Algae EC50)
Maximum LogKow: 8.0 (ChV)
Maximum Mol Wt: 1000

Ethylenediamine Phosphate Green Screen Evaluation Prepared By:



Christopher E. Schlosser, M.F.S.
Associate Toxicologist
ToxServices LLC

Ethylenediamine Phosphate Green Screen Evaluation QC'd By:



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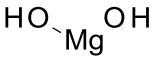
APPENDIX IX F: GREEN SCREEN FOR MAGNESIUM HYDROXIDE (CAS #1309-42-8)[15]

Also Called: 200-06H, Alcanex NHC 25, Asahi Glass 200-06, Baschem 12, CCRIS 3342, Combustrol 500, DP 393, DSB 100, Duhor, Duhor N, EINECS 215-170-3, Ebson RF, FloMag H, FloMag HUS, HSDB 659, Hydro-mag MA, Hydrofy G 1.5, Hydrofy G 2.5, Hydrofy N, KX 8S(A), KX 8S(B), Ki 22-5B, Kisuma 4AF, Kisuma 5, Kisuma 5A, Kisuma 5B, Kisuma 5B-N, Kisuma 5BG, Kisuma 5E, Kisuma 78, Kisuma S 4, Kyowamag F, Lycal 96 HSE, Mag Chem MH 10, Magmesia hydrate, MagneClear 58, Magnesia magma, Magnesia, [milk of], Magnesiamaito, Magnesium dihydroxide, Magnesium hydroxide, Magnesium hydroxide ($Mg(OH)_2$), Magnesium hydroxide gel, Magnesium oxide ($Mg(OH)_2$), Magnesium(II) hydroxide, Magnifin H 10, Magox, Marinco H, Marinco H 1241, Martinal VPF 8812, Milk of magnesia, Milmag, Mint-O-Mag, Nemalite, Oxaine M, Phillips Magnesia Tablets, Phillips Milk of Magnesia Liquid, Reachim, S/G 84, Star 200, UNII-NBZ3QY004S, Versamag

Chemical Structure of Magnesium Hydroxide:



***Note:** Data gaps for this chemical were addressed by using other structurally similar magnesium salts such as magnesium chloride, magnesium lactate, and magnesium citrate. These chemicals in particular were selected due to the fact they are expected to dissociate in stomach acid and because they have been used in other risk assessments as surrogates for magnesium hydroxide (NAS 2000, U.S. EPA 2008).

For Inorganic Chemicals:
Define Form & Physiochemical Properties

7. Particle size (e.g. silica of respirable size) – n/a
8. Structure (e.g. amorphous vs. crystalline) – n/a
9. Mobility (e.g. Water solubility, volatility) – 0.009 g/L at 18°C (Hodgman 1959); 0.04 g/L at 100°C (Hodgman 1959)

Identify Applications/Functional Uses: Flame retardant

Green Screen Rating[16]: Magnesium hydroxide was assigned a Benchmark Score of 2 based on a very High persistence (P) rating and a Moderate corrosion (Cr) rating (2c).

Green Screen (Version 1.0) Levels of Concern for Magnesium Hydroxide														
Human – Tier 1					Human – Tier 2				Eco		Fate		Physical	
C	M	R/D	ED	N	AT	Cr	Sn	ST	AA	CA	P	B	Ex	F
L	L	L	nd	*L*	L	M	*L*	M	L	L	vH	L	L	L

*Endpoints in italics were assigned using estimated values and professional judgment (Structure Activity Relationships).

[15] CPA recommends independent third-party validation of all Green Screen assessments. No independent third-party validation has been done for this assessment . Companies may not make marketing claims based on a Green Screen assessment that has not undergone an independent validation.

[16] For inorganic chemicals with low human and ecotoxicity across all hazard endpoints and low bioaccumulation, persistence alone will not be deemed problematic. Inorganic chemicals that are only persistent will be evaluated under the criteria for Benchmark 4.

Transformation Products and Ratings:
Identify relevant fate and transformation products (i.e., dissociation products, transformation products, valence states) **and/or moieties of concern**[17]

Life Cycle Stage	Transformation Pathway	Transformation Products	CAS #	Green Screen Rating
End of Life	Hydrolysis	Water	7732-18-5	4
End of Life	Hydrolysis	Magnesium	7439-95-4	Not present on the Red List of Chemicals (CPA 2009)
End of Life	Hydrolysis	Hydrogen peroxide	7722-84-1	Not present on the Red List of Chemicals (CPA 2009)

*The above transformation products were screened against the CPA's table of Red List chemicals; none were found.

Introduction

Magnesium hydroxide is commonly used as an antacid and is the active ingredient in the laxative, milk of magnesia (NAS 2000). Additionally, it is used as a residual fuel-oil additive, an alkali drying agent in food, a color-retention agent, and is an ingredient of tooth (NAS 2000). $Mg(OH)_2$ is used as a flame retardant (FR) in commercial furniture applications in the United States and in commercial and residential furniture in the United Kingdom (Fire Retardant Chemicals Association 1998). The stability of $Mg(OH)_2$ at temperatures above 300°C allows it to be incorporated into several polymers (IPCS 1997).

Human Health – Tier 1

Carcinogenicity (C) Score (H, M or L): L
Magnesium hydroxide was assigned a score of Low for carcinogenicity due to findings from several animal studies.

- Not listed as a known carcinogen by IARC, NTP, U.S. EPA, or CA Prop 65.
- Oncologic results predict the hazard rating for carcinogenicity for magnesium hydroxide to be low (OncoLogic 2005).
- The incidence of all cancers among 2,391 Norwegian males who worked between 1951 and 1974 in a factory producing magnesium metal was not significantly increased when compared with cancer incidence for the Norwegian nation population of the same age. The number of cases of lip as well as stomach and lung cancers was significantly increased. Workers in this study were also

[17] A moiety is a discrete chemical entity that is a constituent part or component of a substance. A moiety of concern is often the parent substance itself for organic compounds. For inorganic compounds, the moiety of concern is typically a dissociated component of the substance or a transformation product.

exposed to magnesium oxide dust, coal dust, chlorine gas, hydrochlorine aerosols, chlorinated aromatics, and sulphur dioxide. Therefore, it is not possible to determine whether exposure to magnesium dust alone is responsible for the observed elevations in cancer incidence (Heldaas 1989).

- Exposure of male Wistar rats to short (4.9x0.31 mm) or long (12x0.44) $MgSO_4 \cdot 3H_2O$ filaments by inhalation (6 hours per day, 5 days per week for 1 year) was not associated with an increase in the incidence of any tumor types in animals sacrificed 1 day or 1 year after cessation of exposure. One year after exposure, one pulmonary adenoma was observed in animals that had been exposed to long filaments for 3 weeks and none in controls. One year after exposure, neoplastic lesions were observed in control animals and short- and long-filament treated rats that had been exposed for 1 year. Two pulmonary adenomas were observed in the exposed animals and one in control animals. No hepatocellular adenomas or carcinomas occurred in controls, one hepatocellular adenoma was found in the long-filament group, and one hepatocellular carcinoma was found in the short-filament group, respectively (Hori 1994).
- Mice fed 0.5% or 2% of aqueous $MgCl_2$ in their diet for 96 weeks (68, or 336 mg/kg-day for males; 87 or 470 mg/kg-day for females) showed no significant change in the incidence of malignant lymphoma and leukemia. Dose-related increases in incidence of malignant lymphoma and leukemia occurred in male mice (controls, five of 50; low dose, seven of 50; high dose, eleven of 50), but not in females (controls, nine of 49; low dose, 17 of 50; high dose, 11 of 50). The incidence of hepatocellular carcinomas in male mice was decreased in a dose-related manner (controls, 13 of 50; low dose, six of 50; high dose, four of 50) and the incidence in high-dose males was significantly different from that in controls. Toxicity in female mice (i.e., decreased body weight) suggests that the study was conducted at or near the maximum tolerated dose (MTD) for females (Kurata 1989).
- Several studies in rats have shown that dietary $Mg(OH)_2$ can protect against chemically induced bowel carcinogenesis by suppressing hyperproliferation of the colon epithelium. Dietary levels of 250 ppm $Mg(OH)_2$ inhibited the incidence of colon adenoma and adenocarcinoma in rats given carcinogens methylazoxymethanol acetate (MAM acetate) or 1, 2-dimethylhydrazine (Tanaka 1989; Morishita 1991; Mori 1993). Administration of $Mg(OH)_2$ in the diet and the bowel carcinogen cholic acid reduced cell proliferation in bowel tissue (Wang 1993). Dietary $Mg(OH)_2$ also prevented the expression of *c-myc* gene in colon mucosa cells of MAM acetate-treated rats (Wang 1993).
- The subcommittee concludes that $Mg(OH)_2$ is not likely to be carcinogenic to humans by the oral route. No adequate data are available to assess the carcinogenicity of $Mg(OH)_2$ by the dermal or inhalation or routes of exposure (NAS 2000).

Mutagenicity (M) and Genotoxicity Score (H, M or L): L

Magnesium hydroxide was assigned a score of Low for mutagenicity based on negative results from several genotoxocity assays.

- $MgCl_2$ was judged to be a non-mutagen in the Ames assay when tested with and without metabolic activation and it did not induce chromosomal aberrations in

Chinese hamster fibroblast cells in vitro (Ishidate 1984). Chromatid gaps, breaks, and exchanges were observed in Chinese hamster lung fibroblasts treated with $MgCl_2$ at concentrations of 8.0 and 12.0 mg/ml but not at or below concentrations of 4 mg/mL (Ashby and Ishidate 1986). Since positive results occurred at only high concentrations, the authors suggest that the clastogenic effects observed may be an artifact induced by hypertonic solutions. $MgCl_2$ did not induce mutations in mouse lymphoma L5178/TK+/− cells at concentrations of 5.7–18.1 mg Mg^{2+}/ml (Amacher and Paillet 1980). MgSO4 was not mutagenic in Salmonella typhimurium (strains TA100, TA1535) and Escherichia coli WP2 uvrA at concentrations of 313–5,000 mg/plate (Oguma 1998). MgSO4 was not mutagenic in Salmonella strain TA98 tested without metabolic activation and strain TA1537 tested with metabolic activation at a concentration of 156–5,000 mg/plate (Oguma 1998).

Reproductive (R) and Developmental (D) Toxicity Score (H, M or L): L
Magnesium hydroxide was assigned a score of Low for reproductive and developmental toxicity based on the results from one animal study and one study in humans.

- No maternal or reproductive effects were observed in a 10 day (GD 6-15) oral reproductive/developmental study on rats using $MgCl_2$. The authors of the study determined the NOAEL to be >96 mg/kg/day for Mg^{2+} (NAS 2000).
- A repeated dose/developmental (3^{rd} trimester) study on humans produced no effect on newborns except slightly increased body weight and hypermagnesiumemia. Cord serum magnesium levels reported to be 70-100% of maternal levels (potentially causing neurological depression in neonate, characterized by respiratory depression, muscle weakness, decreased reflexes). Prolonged magnesium treatment during pregnancy may be associated with maternal and fetal hypocalcemia and adverse effects on fetal bone mineralization (HSDB 2003).

Endocrine Disruption (ED) Score (H, M or L): nd

- Not listed as a potential endocrine disruptor on the EU Priority List of Suspected Endocrine Disruptors.
- Not listed as a potential endocrine disruptor on the OSPAR List of Chemicals of Possible Concern.
- Not listed as a potential endocrine disruptor on the Red List of Chemicals (CPA 2009).
- No other relevant endocrine disruption data could be identified for magnesium hydroxide.

Neurotoxicity (N) Score (H, M or L): *L*
Magnesium hydroxide was assigned a score of Low for neurotoxicity based on professional judgement.

- Not classified as a developmental neurotoxicant (Grandjean and Landrigan 2006).
- Not listed as a potential neurotoxicant on the Red List of Chemicals (CPA 2009).
- Magnesium hydroxide is expected to be of low hazard for neurotoxicity based on professional judgment (U.S. EPA 2008).

Human Health – Tier 2

Acute Mammalian (AT) Toxicity Score (H, M or L): L
Magnesium hydroxide was assigned a score of Low for acute mammalian toxicity based on oral LD_{50} values greater than 2,000 mg/kg-bw. This score is based on data from one route of exposure in two different species of animals.

- *Oral*: An LD_{50} of 8,500 mg/kg was determined in the rat (Lewis 2000).
- *Oral*: An LD_{50} of 8,500 mg/kg was determined in the mouse (Lewis 2000)

Corrosion/Irritation (Skin/ Eye) (Cr) Score (H, M or L): M
Magnesium hydroxide was assigned a score of Moderate for corrosion/irritation based on the substance being moderately irritating to the eyes of rabbits.

- *Dermal*: No relevant data were identified for magnesium hydroxide.
- *Ocular*: Moderately irritating to rabbit eyes (IUCLID 2000).
- *Ocular*: Administration of milk of magnesia twice a day for 3-4 days caused damage to corneal epithelium of rabbit eyes; however, effects disappeared within 2-3 days. No additional details were provided (HSDB 2003).

Sensitization (Sn) Score (Skin and Respiratory) (H, M or L): *L*
Magnesium hydroxide was assigned a score of Low for sensitization based on professional judgment.

- Magnesium hydroxide is not expected to cause skin sensitization based on professional judgment. No other details were provided (U.S. EPA 2008).

Systemic/ Organ (ST) Toxicity Score (includes organ effects and immunotoxicity) (H, M or L): M
Magnesium hydroxide was assigned a score of Moderate for systemic/organ toxicity based on suggestive animal studies.

- No human studies were found that investigated the toxic effects of $Mg(OH)_2$ following inhalation exposure. Exposure of male Wistar rats to short (4.9x0.31 mm) or long (12x0.44 mm) $MgSO_4/5Mg(OH)_2 \cdot 3H_2O$ filaments inhalation, 6 hours per day, 5 days per week for up to a year was associated with a slight increase in the incidence of pulmonary lesions 1 year after cessation of exposure. A year after cessation of exposure, histopathological examination of treated animals revealed a slight increase in segmental calcification of the pulmonary artery and thickening of the lung pleura in rats exposed to either short or long filaments for 4 week or 1 year. Differences between exposed and unexposed animals were statistically significant. No significant differences in body, lung, liver, kidney, or spleen weights were detected between animals sacrificed 1 day or 1 year after a 1 year exposure to short or long filaments. No significant differences in survival were observed between animals sacrificed 1 day or 1 year after a 1 year exposure to short or long filaments (Hori 1994).
- In its review of clinical studies, the Institute of Medicine (IOM 1997) concluded that Mg^{2+} in the diet is never high enough to cause adverse effects. The IOM set a "tolerable upper intake level" (TUL) for the ingestion of magnesium (Mg^{2+}) supplements of 5 mg/day for anyone over 1 year old. The TUL was based on the

approximate no-observed-adverse-effects level (NOAEL) for osmotic diarrhea in humans reported by Marken (1989), Fine (1991), Ricci (1991), and Bashir (1993). Five of the six patients reported epigastric burning or distension and two reported diarrhea.

- Decreased body weight was found to be the critical effect in B6C2F1 mice fed diets containing 0%, 0.3%, 0.6%, 1.25%, 2.5%, or 5% $MgCl_2 \cdot 6H_2O$ for 13 weeks. Intake of Mg^{2+} added to the diet was calculated to be 73, 146, 322, 650, or 1,368 mg/kg-day in treated males and 92, 190, 391, 817, and 1,660 mg/kg-day in treated females (the amount of magnesium in the basal diet was not provided). The 5% treatment group of both sexes showed a significant decrease in weight gain (15% in males and 10% in females). Males in the 2.5 and 5% group exhibited an increased incidence of renal tubular vacuolation. The authors determined that the LOAEL for this study was 650 mg/kg-day (Tanaka 1994).
- Decreased body weight and increased renal vacuolation were observed in male, but not female B6C3F1 mice fed a diet that contained 5% $MgCl_2 \cdot 6H_2O$ (Mg^{2+} at 840 mg/kg-day) for 13 weeks. No treatment-related effects were reported for male and female mice fed a diet containing 0, 0.3, 0.6, 1.25 or 2.5% $MgCl_2 \cdot 6H_2O$ for 13 weeks. The NOAEL for Mg^{2+} in this study was determined to be 587 mg/kg-day for females and 420 mg/kg-day for males (Kurata 1989).
- Decreased body weight gain (about 25% at termination of the exposure) and increases in relative brain, heart, and kidney weights compared with controls were observed in female B6C3F1 mice fed diets for 96 weeks that contained 2% $MgCl_2 \cdot 6H_2O$ (470 mg Mg^{2+}/kg-day). No treatment-related effects were observed in male mice fed diets that contained 0.5% or 2% of $MgCl_2 \cdot 6H_2O$ (68 or 336 mg/kg-day) or female mice fed diets that contained 0.5% of $MgCl_2 \cdot 6H_2O$ (87 mg/kg-day) for 96 weeks. Histopathological examination after 104 weeks of exposure revealed no treatment-related changes. Urinary, hematological, and clinical chemistry parameters and histopathological measures were not affected by treatment, except for a significant increase in serum albumin in high-dose females. Survival rates were comparable between treated and control animals. The LOAEL for this study is 470 mg/kg-d based on the treatment-related effects in high-dose female mice (Kurata 1989).

Ecotoxicity

Acute Aquatic (AA) Toxicity Score (H, M or L): L

Magnesium hydroxide was assigned a score of Low for acute aquatic toxicity based on LC_{50} values greater than 100 mg/L.

- An LC_{50} of 1,110 mg/L was estimated in fish (species not specified) (fish, 96 hour) from the measured LC_{50}s for $MgCl_2$ and $MgSO_4$, modified by a molecular weight adjustment for $Mg(OH)_2$ (Mount 1997).
- An LC_{50} of 648 mg/L was estimated in daphnia (species not identified) (daphnid, 48 hour) from the measured LC_{50}s for $MgCl_2$ and $MgSO_4$, modified by a molecular weight adjustment for $Mg(OH)_2$ (Mount 1997; Biesinger and Christensen 1972).

- An EC_{50} of 2,111 mg/L was estimated in green algae (species not identified) (green algae, 96 hour) by using an acute to chronic ratio of 4 (U.S. EPA 2008).

Chronic Aquatic (CA) Toxicity Score (H, M or L): L
Magnesium hydroxide was assigned a score of Low for chronic aquatic toxicity based on ChV values greater than 10 mg/L.

- A ChV of 403 mg/L was estimated in fish (species not identified) (fish, time not identified) using an acute to chronic ratio of 3.3. This ratio is for daphnids and has not been validated for use with fish (U.S. EPA 2008).
- A ChV of 197 mg/L was estimated in daphnia (species not identified, length of time not identified) from the measured ChV for Mg^{2+} ion, modified by a molecular weight adjustment for $Mg(OH)_2$ (Suter 1996).
- A ChV of 528 mg/L was estimated in green algae (species not identified, length of time not identified) from the measured NOEC and LOEC for $MgSO_4$, modified by a molecular weight adjustment for $Mg(OH)_2$ (ECOTOX Database undated).

Environmental Fate

Persistence (P) Score (vH, H, M, or L): vH
Magnesium hydroxide was assigned a score of very High for persistence based on its inability to biodegrade in the environment.

- As a fully oxidized inorganic material, magnesium hydroxide is not expected to biodegrade, oxidize in air, or undergo hydrolysis under environmental conditions. Magnesium hydroxide does not absorb light at environmentally relevant wavelengths and is not expected to photolyze. No degradation processes for magnesium hydroxide under typical environmental conditions were identified. Chemical is identified as recalcitrant (U.S. EPA 2008).

Bioaccumulation (B) Score (vH, H, M, or L): L
Magnesium hydroxide was assigned a score of Low for bioaccumulation based on a BCF value less than 500.

- Magnesium hydroxide is not expected to be bioaccumulative based on an estimated BCF of <500 (U.S. EPA 2008).

Physical Properties

Explosivity (Ex) Hazard Rating (H, M or L): L
Magensium hydroxide was assigned a score of Low for explosivity because no basis for concern was identified.

- Magnesium hydroxide is not explosive (IUCLID 2000).

Flammability (F) Hazard Rating (H, M or L): L
Magensium hydroxide was assigned a score of Low for fammability because no basis for concern was identified.

- Magnesium hydroxide is not flammable (IUCLID 2000).

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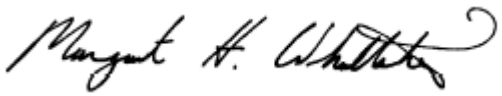

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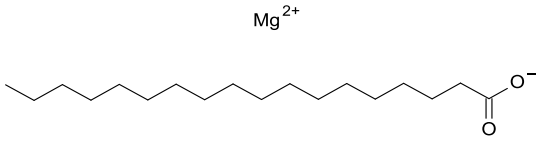
APPENDIX IX G: GREEN SCREEN FOR MAGNESIUM STEARATE (CAS #557-04-0)[18]

Also Called: Magnesium octadecanoate, Magnesium stearate, Magnesium stearate [JAN], Octadecanoic acid, magnesium salt, AI3-01638, Dibasic magnesium stearate, EINECS 209-150-3, HSDB 713, Magnesium distearate, Magnesium octadecanoate, Magnesium stearate, NP 1500, NS-M (salt), Octadecanoic acid, magnesium salt, Petrac MG 20NF, SM 1000, SM-P, Stearic acid, magnesium salt, Synpro 90, Synpro Magnesium Stearate 90, UNII-70097M6I30

Chemical Structure of Magnesium Stearate:



For Inorganic Chemicals:
Define Form & Physiochemical Properties

10. Particle size (e.g. silica of respirable size) – n/a
11. Structure (e.g. amorphous vs. crystalline) – Fine, white powder (HSDB 2009)
12. Mobility (e.g. Water solubility, volatility) – Not soluble in water (NIOSH 1994); soluble in hot alcohol (Mallinckodt Chemicals 2009).

Identify Applications/Functional Uses: Flame retardant

Green Screen Rating[19]: Magnesium stearate was assigned a Benchmark Score of 2 based on its High persistence (P) and Moderate irritation/corrosion (Cr) and systemic/organ toxicity (ST) (2c).

Green Screen (Version 1.0) Levels of Concern for Magnesium Stearate														
Human – Tier 1					Human – Tier 2				Eco		Fate		Physical	
C	M	R/D	ED	N	AT	Cr	Sn	ST	AA	CA	P	B	Ex	F
L	L	L	nd	nd	L	M	L	M	*L*	*M*	H	L	M	H

*Endpoints in italics were assigned using estimated values and professional judgment (Structure Activity Relationships).

[18] CPA recommends independent third-party validation of all Green Screen assessments. No independent third-party validation has been done for this assessment . Companies may not make marketing claims based on a Green Screen assessment that has not undergone an independent validation.

[19] For inorganic chemicals with low human and ecotoxicity across all hazard endpoints and low bioaccumulation, persistence alone will not be deemed problematic. Inorganic chemicals that are only persistent will be evaluated under the criteria for Benchmark 4.

Transformation Products and Ratings:
Identify relevant fate and transformation products (i.e., dissociation products, transformation products, valence states) **and/or moieties of concern**[20]

Life Cycle Stage	Transformation Pathway	Transformation Products	CAS #	Green Screen Rating
End of Life	Dissociation	Magnesium	7439-95-4	Not present on the Red List of chemicals (CPA 2009)
End of Life	Dissociation	Octadecanoic acid	57-11-4	Not present on the Red List of chemicals (CPA 2009)
End of Life	Combustion	Carbon monoxide	630-08-0	Reproductive/developmental toxicant, neurotoxicant (CPA 2009)
End of Life	Combustion	Carbon dioxide	124-38-9	Not present on the Red List of chemicals (CPA 2009)
End of Life	Combustion	Magnesium oxide	1309-48-4	Not present on the Red List of chemicals (CPA 2009)

*The above transformation products were screened against the CPA's table of Red List chemicals (CPA 2009).

Introduction

Magnesium stearate is used as a filler material and binder in drug tablets and as an emulsification agent in cleansing products and cosmetics (HSDB 2009). Because the chemical is commonly used in pharmaceuticals, it has been listed as Generally Recognized as Safe (GRAS) by the FDA (U.S. FDA 2010).

The National Institute of Occupational Safety and Health have established a threshold limit value (TLV) for magnesium stearate of 10 mg/m^3 and the Occupational Safety and Health Administration assigned a permissible exposure limit (PEL) of 15 mg/m^3 (NIOSH 1994, Mallinckrodt Chemicals 2009).

Human Health – Tier 1

Carcinogenicity (C) Score (H, M or L): L

Magnesium stearate was assigned a score of Low for carcinogenicity because no basis for concern was identified.

- Not listed as a known carcinogen by IARC, NTP, U.S. EPA or CA Prop 65.
- A4- Not classifiable as a human carcinogen (HSDB 2009).

[20] A moiety is a discrete chemical entity that is a constituent part or component of a substance. A moiety of concern is often the parent substance itself for organic compounds. For inorganic compounds, the moiety of concern is typically a dissociated component of the substance or a transformation product.

Mutagenicity (M) and Genotoxicity Score (H, M or L): L
Magnesium stearate was assigned a score of Low for mutagenicity based on a negative Ames assay results.

- Magnesium stearate tested negative in an Ames assay (concentrations and strains not reported) both with and without metabolic activation (Litton Bionetics 1976).

Reproductive (R) and Developmental (D) Toxicity Score (H, M or L): L
Magnesium stearate was assigned a score of Low for reproductive and developmental toxicity based on negative test results in rabbits.

- Magnesium stearate did not induce developmental effects in orally treated pregnant rabbits (no other detail provided) (U.S. EPA 2009b).
- A vehicle containing 5.5% magnesium stearate did not induce any teratogenic effects at doses of 2.5 mg/kg when administered orally to pregnant rabbits (no other details provided) (Gottschewshi 1967).

Endocrine Disruption (ED) Score (H, M or L): nd

- Magnesium stearate is not listed as a potential endocrine disruptor on the EU Priority List of Suspected Endocrine Disruptors.
- Magnesium stearate is not listed as a potential endocrine disruptor on the OSPAR List of Chemicals of Possible Concern.
- Magnesium stearate is not listed as a potential endocrine disruptor on the Red List of Chemicals (CPA 2009).

Neurotoxicity (N) Score (H, M or L): nd

- Magnesium stearate is not classified as a developmental neurotoxicant (Grandjean and Landrigan 2006).
- Magnesium stearate is not listed as a potential neurotoxicant on the Red List of Chemicals (CPA 2009).

<u>Human Health – Tier 2</u>

Acute Mammalian (AT) Toxicity Score (H, M or L): L
Magnesium stearate was assigned a score of Low for acute mammalian toxicity based on an oral LD_{50} greater than 2,000 mg/kg-bw. Data is based on studies from one route of exposure in one species of animals.

- *Oral*: An LD_{50} of >10,000 mg/kg-bw was established in the rat (U.S. EPA 2009b).

Corrosion/ Irritation (Skin/ Eye) (Cr) Score (H, M or L): M
Magnesium stearate was assigned a score of Moderate for corrosion and irritation based on conflicting results.

- *Dermal*: Magnesium stearate is a slight skin irritant (Science Lab 2008).
- *Ocular*: Magnesium stearate is slightly hazardous in the case of eye contact (Natural Sourcing 2009).

Sensitization (Sn) Score (Skin and Respiratory) (H, M or L): L
Magnesium stearate was assigned a score of Low for sensitization based on negative test results.

- Magnesium stearate is does not induce dermal sensitization (no other details provided) (U.S. EPA 2009b).

Systemic/ Organ (ST) Toxicity Score (includes organ effects and immunotoxicity) (H, M or L): M
Magnesium stearate was assigned a score of Moderate for systemic/organ toxicity based on results from animal studies.

- Magnesium stearate was fed to groups of 20 male and 20 female rats (strain not reported) at levels of 0, 5, 10 and 20% in a semisynthetic diet for 3 months. Decreased weight gain was found in males in the 20% group. Urolithiasis was found in 8 males and in 7 females in the same group. Reduced relative liver weight was seen in males in the 10% and in the 20% groups, and an increased amount of iron was found in the livers of the 20% group. Nephrocalcinosis was reduced in females in the 20% group. In this experiment the no-effect-level is estimated to be 5% magnesium stearate in the diet, corresponding to 2,500 mg/kg bw/day (Sondergaard 1980).
- Magnesium stearate did not induce any adverse effects in rats when treated orally with 500 mg/kg/day for 13 months (no other details provided) (U.S. EPA 2009b).
- Magnesium stearate targets the liver and skin (Science Lab 2008).
- Repeated or prolonged exposure to magnesium stearate can produce target organs damage (Science Lab 2008).
- Grossly excessive and chronic inhalation of the dust may cause a progressive chemical pneumonitis, cyanosis, and pulmonary edema (Mallinckrodt Chemicals 2009).

Ecotoxicity

Acute Aquatic (AA) Toxicity Score (H, M or L): *L*
Magnesium stearate was assigned a score of Low for acute aquatic toxicity based on professional opinion.

- ECOSAR was unable to predict E/LC_{50} values for magnesium stearate due to its low solubility.
- Magnesium stearate is classified as a neutral organic.

Chronic Aquatic (CA) Toxicity Score (H, M or L): *M*
Magnesium stearate was assigned a score of Moderate for chronic aquatic toxicity based on GHS's recommendation.

- ECOSAR was unable to predict ChV values for magnesium stearate due to its low solubility.

Environmental Fate

Persistence (P) Score (vH, H, M, or L): H
Magnesium stearate was assigned a score of High for persistence based on its inability to biodegrade and a half life between 60 and 180 days in soil.

- The products of degradation are more toxic than the parent compound (Science Lab 2008).
- EPI Suite – BIOWIN model results indicate magnesium stearate is not readily biodegradable, and has a predicted degradation time of days to month. STP removal expected using BIOWIN/EPA Draft Method results indicate approximately 99% total removal, with approximately 37% due to biodegradation. Fugacity III modeling predicts approximately 84% partitioning to soil with a half-life of 75 days, and approximately 16% partitioning to water with a half-life of 38 days (U.S. EPA 2010).

Bioaccumulation (B) Score (vH, H, M, or L): L
Magnesium stearate was assigned a score of Low for bioaccumulation based on a BAF less than 500.

- BCFBAF predicts a bioaccumulation factor (BAF) of 7.079 and a log K_{ow} of 14.44 (U.S. EPA 2009a).

Physical Properties

Explosivity (Ex) Hazard Rating (H, M or L): M
Magnesium stearate was assigned a score of Moderate for explosivity based on its ability to explode when in powder form.

- Dust explosion possible if in powder or granular form and mixed with air (NIOSH 1994).

Flammability (F) Hazard Rating (H, M or L): H
Magnesium stearate was assigned a score of High for flammability based on it being combustible.

- Magnesium stearate is spontaneously combustible (HSDB 2009).
- Magnesium stearate may be combustible at high temperatures (Science Lab 2008).

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EPI Suite Results for Magnesium Stearate:

CAS Number: 557-04-0
SMILES : [Zn](OC(=O)CCCCCCCCCCCCCCCCC)OC(=O)CCCCCCCCCCCCCCCCC
CHEM : Zinc stearate
MOL FOR: C36 H70 O4 Zn1
MOL WT : 632.35
---------- EPI SUMMARY (v4.00) ----------
Physical Property Inputs:
Log Kow (octanol-water): ------
Boiling Point (deg C) : ------
Melting Point (deg C) : ------
Vapor Pressure (mm Hg) : ------
Water Solubility (mg/L): ------
Henry LC (atm-m3/mole) : ------

Log Octanol-Water Partition Coef (SRC):
Log Kow (KOWWIN v1.67 estimate) = 14.44

Boiling Pt, Melting Pt, Vapor Pressure Estimations (MPBPVP v1.43):
Boiling Pt (deg C): 675.43 (Adapted Stein & Brown method)
Melting Pt (deg C): 294.55 (Mean or Weighted MP)
VP(mm Hg,25 deg C): 2.71E-015 (Modified Grain method)
VP (Pa, 25 deg C) : 3.61E-013 (Modified Grain method)
MP (exp database): 250 deg C
Subcooled liquid VP: 7.56E-013 mm Hg (25 deg C, Mod-Grain method)
: 1.01E-010 Pa (25 deg C, Mod-Grain method)

Water Solubility Estimate from Log Kow (WSKOW v1.41):
Water Solubility at 25 deg C (mg/L): 4.609e-011
log Kow used: 14.44 (estimated)
no-melting pt equation used

Water Sol Estimate from Fragments:
Wat Sol (v1.01 est) = 6.3235e-007 mg/L

ECOSAR Class Program (ECOSAR v1.00):
Class(es) found: Neutral Organics

Henrys Law Constant (25 deg C) [HENRYWIN v3.20]:
Bond Method : Incomplete
Group Method: Incomplete
For Henry LC Comparison Purposes:
User-Entered Henry LC: not entered
Henrys LC [via VP/WSol estimate using User-Entered or Estimated values]:
HLC: 4.892E-005 atm-m3/mole (4.957E+000 Pa-m3/mole)
VP: 2.71E-015 mm Hg (source: MPBPVP)
WS: 4.61E-011 mg/L (source: WSKOWWIN)

Log Octanol-Air Partition Coefficient (25 deg C) [KOAWIN v1.10]:
Can Not Estimate (can not calculate HenryLC)

Probability of Rapid Biodegradation (BIOWIN v4.10):
Biowin1 (Linear Model) : 0.6634
Biowin2 (Non-Linear Model) : 0.0925
Expert Survey Biodegradation Results:
Biowin3 (Ultimate Survey Model): 2.3984 (weeks-months)

Biowin4 (Primary Survey Model) : 3.4736 (days-weeks)
MITI Biodegradation Probability:
Biowin5 (MITI Linear Model) : 0.4130
Biowin6 (MITI Non-Linear Model): 0.1249
Anaerobic Biodegradation Probability:
Biowin7 (Anaerobic Linear Model): 0.8732
Ready Biodegradability Prediction: NO

Hydrocarbon Biodegradation (BioHCwin v1.01):
Structure incompatible with current estimation method!

Sorption to aerosols (25 Dec C)[AEROWIN v1.00]:
Vapor pressure (liquid/subcooled): 1.01E-010 Pa (7.56E-013 mm Hg)
Log Koa (): not available
Kp (particle/gas partition coef. (m3/ug)):
Mackay model : 2.98E+004
Octanol/air (Koa) model: not available
Fraction sorbed to airborne particulates (phi):
Junge-Pankow model : 1
Mackay model : 1
Octanol/air (Koa) model: not available

Atmospheric Oxidation (25 deg C) [AopWin v1.92]:
Hydroxyl Radicals Reaction:
OVERALL OH Rate Constant = 42.9098 E-12 cm3/molecule-sec
Half-Life = 0.249 Days (12-hr day; 1.5E6 OH/cm3)
Half-Life = 2.991 Hrs
Ozone Reaction:
No Ozone Reaction Estimation
Fraction sorbed to airborne particulates (phi):
1 (Junge-Pankow, Mackay avg)
not available (Koa method)
Note: the sorbed fraction may be resistant to atmospheric oxidation

Soil Adsorption Coefficient (KOCWIN v2.00):
Koc : 8.35E+007 L/kg (MCI method)
Log Koc: 7.922 (MCI method)
Koc : 2.843E+008 L/kg (Kow method)
Log Koc: 8.454 (Kow method)

Aqueous Base/Acid-Catalyzed Hydrolysis (25 deg C) [HYDROWIN v2.00]:
Rate constants can NOT be estimated for this structure!

Bioaccumulation Estimates (BCFBAF v3.00):
Log BCF from regression-based method = 0.500 (BCF = 3.162 L/kg wet-wt)
Log Biotransformation Half-life (HL) = 2.6112 days (HL = 408.5 days)
Log BCF Arnot-Gobas method (upper trophic) = -0.048 (BCF = 0.8945)
Log BAF Arnot-Gobas method (upper trophic) = 0.850 (BAF = 7.079)
log Kow used: 14.44 (estimated)

Volatilization from Water:
Henry LC: 4.89E-005 atm-m3/mole (calculated from VP/WS)
Half-Life from Model River: 32.66 hours (1.361 days)
Half-Life from Model Lake : 567.2 hours (23.63 days)

Removal In Wastewater Treatment:
Total removal: 94.04 percent

Total biodegradation: 0.78 percent
Total sludge adsorption: 93.26 percent
Total to Air: 0.00 percent
(using 10000 hr Bio P,A,S)

Removal In Wastewater Treatment (recommended maximum 95%):
Total removal: 99.07 percent
Total biodegradation: 37.17 percent
Total sludge adsorption: 61.89 percent
Total to Air: 0.00 percent
(using Biowin/EPA draft method)

Level III Fugacity Model:

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	0.177	5.98	1000
Water	15.9	900	1000
Soil	83.9	1.8e+003	1000
Sediment	0.00575	8.1e+003	0

Persistence Time: 1.21e+003 hr

ECOSAR Results for Magnesium Stearate:

SMILES : [Mg](OC(=O)CCCCCCCCCCCCCCCCC)OC(=O)CCCCCCCCCCCCCCCCC
CHEM : Octadecanoic acid, magnesium salt
CAS Num: 000557-04-0
ChemID1:
ChemID2:
ChemID3:
MOL FOR: C36 H70 O4 Mg1
MOL WT : 591.26
Log Kow: 14.34 (KowWin estimate)
Melt Pt:
Wat Sol: 1.045E-010 mg/L (WskowWin estimate)

ECOSAR v1.00 Class(es) Found

Neutral Organics

ECOSAR Class	Organism	Duration	End Pt	Predicted mg/L (ppm)
Neutral Organics	: Fish	96-hr	LC50	6.35e-009 *
Neutral Organics	: Fish	14-day	LC50	7.83e-009 *
Neutral Organics	: Daphnid	48-hr	LC50	2.22e-008 *
Neutral Organics	: Green Algae	96-hr	EC50	2.23e-006 *
Neutral Organics	: Fish	30-day	ChV	1.51e-009 *
Neutral Organics	: Daphnid		ChV	1.82e-008 *
Neutral Organics	: Green Algae		ChV	6.68e-006 *
Neutral Organics	: Fish (SW)	96-hr	LC50	3.46e-009 *
Neutral Organics	: Mysid Shrimp	96-hr	LC50	9.53e-013
Neutral Organics	: Fish (SW)		ChV	1.11e-006 *
Neutral Organics	: Mysid Shrimp (SW)		ChV	2.13e-015
Neutral Organics	: Earthworm	14-day	LC50	54.019 *

Note: * = asterisk designates: Chemical may not be soluble

enough to measure this predicted effect.

Neutral Organics:

For Fish LC50 (96-h), Daphnid LC50, Mysid: If the log Kow is greater than 5.0, or if the compound is solid and the LC50 exceeds the water solubility by 10X, no effects at saturation are predicted.

For Fish LC50 (14-day) and Earthworm LC50: If the log Kow is greater than 6.0, or if the compound is solid and the LC50 exceeds the water solubility by 10X, no effects at saturation are predicted.

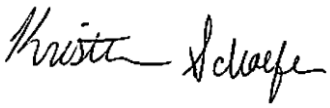
For Green Algae Acute Toxicity Values: If the log Kow of the chemical is greater than 6.4, or if the compound is solid and the EC50 exceeds the water solubility by 10X, no effects at saturation are predicted for these endpoints.

For All Chronic Toxicity Values: If the log Kow of the chemical is greater than 8.0, or if the compound is solid and the ChV exceeds the water solubility by 10X, no effects at saturation are predicted for these endpoints.

ECOSAR v1.00 SAR Limitations:

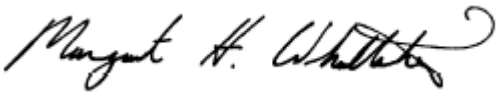
Maximum LogKow: 5.0 (Fish 96-hr LC50; Daphnid LC50, Mysid LC50)
Maximum LogKow: 6.0 (Fish 14-day LC50; Earthworm LC50)
Maximum LogKow: 6.4 (Green Algae EC50)
Maximum LogKow: 8.0 (ChV)
Maximum Mol Wt: 1000

Magnesium Stearate Green Screen Evaluation Prepared By:



Kristen Schaefer, M.F.S.
Associate Toxicologist
ToxServices LLC

Magnesium Stearate Green Screen Evaluation QC'd By:



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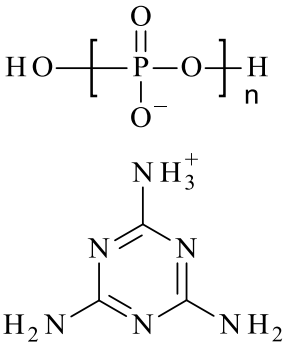
Managing Director and Chief Toxicologist
ToxServices LLC

APPENDIX IX H: GREEN SCREEN FOR MELAMINE POLYPHOSPHATE (CAS #218768-84-4)[21]

Also Called: Polyphosphoric acids, compounds with melamine, Melapur 200

Chemical Structure of Melamine Polyphosphate:



***Note:** Data gaps for melamine polyphosphate (CAS #218768-84-4) were addressed using the structurally similar chemicals melamine phosphate (CAS #41583-09-9), melamine (CAS #108-78-1), and phosphate (CAS #14265-44-2) as surrogates.

For Polymers (Identify Monomers and Corresponding Properties):
% of Each Monomer – n/a
Are the monomers blocked? (Y/N) – n/a
Molecular Weight (MW) of Polymer >1,000 (U.S. EPA 2008b)
% of Polymer with – n/a
a) MW <500
b) MW <1,000
% Weight Residual Monomers – n/a
Solubility/Dispersability/Swellability – 20 g/L (U.S. EPA 2008b)
Particle Size – n/a
Overall Polymer Charge – n/a

Identify Applications/Functional Uses: Flame retardant.

Green Screen Rating[22]: Melamine polyphosphate was assigned a Benchmark Score of 2 based on High systemic toxicity (ST), and Moderate carcinogenicity (C) and mutagenicity (M) (2d).

Green Screen (Version 1) Levels of Concern for Melamine Polyphosphate														
Human – Tier 1					Human – Tier 2				Eco		Fate		Physical	
C	**M**	**R/D**	**ED**	**N**	**AT**	**Cr**	**Sn**	**ST**	**AA**	**CA**	**P**	**B**	**Ex**	**F**
M	*M*	**L**	nd	nd	**L**	**L**	*L*	*H*	*L*	*L*	*M*	**L**	**L**	**L**

[21] CPA recommends independent third-party validation of all Green Screen assessments. No independent third-party validation has been done for this assessment . Companies may not make marketing claims based on a Green Screen assessment that has not undergone an independent validation.
[22] For inorganic chemicals with low human and ecotoxicity across all hazard endpoints and low bioaccumulation, persistence alone will not be deemed problematic. Inorganic chemicals that are only persistent will be evaluated under the criteria for Benchmark 4.

*Endpoints in italics were assigned using estimated values and professional judgment (Structure Activity Relationships).

Transformation Products and Ratings:
Identify relevant fate and transformation products (i.e., dissociation products, transformation products, valence states) and/or moieties of concern[23]

Life Cycle Stage	Transformation Pathway	Transformation Products	CAS #	Green Screen Rating
End of Life	Combustion; Biodegradation	Melamine	108-78-1	Not present on Red List of Chemicals (CPA 2009)
End of Life	Combustion; Biodegradation	Phosphate ion	14265-44-2	Not present on Red List of Chemicals (CPA 2009)
End of Life	Combustion	Melamine pyrophosphate	15541-60-3	Not present on Red List of Chemicals (CPA 2009)
End of Life	Combustion	Phosphoric acid	7664-38-2	Not present on Red List of Chemicals (CPA 2009)
End of Life	Combustion	Hydrogen cyanide	74-90-8	Potential neurotoxicant (CPA 2009)
End of Life	Combustion	Melamine polyphosphates	20208-95-1	Not present on Red List of Chemicals (CPA 2009)

*The above transformation products were screened against the CPA's table of Red List chemicals.

Introduction

Melamine phosphates are salts of melamine and phosphoric acid. These salts have good properties of thermal stability and are commonly used as flame retardants (UNEP 1997). Melamine and its derivatives (cyanurate, phosphates) are currently used in flexible polyurethane foams, intumescent coatings, polyamides and thermoplastic polyurethanes. There were not extensive data for melamine polyphosphate. In cases of data gaps, data for melamine phosphate, and the ions for melamine and phosphate were considered.

The U.S Food and Drug Administration (U.S. FDA) established a TDI (Tolerable Daily Intake) for melamine of 0.63 mg/kg bw/day (U.S. FDA 2007). This TDI was based on the results of a 13-week rat study of melamine (see reproductive toxicity section) and incorporates safety factors totaling 100. There is recent, strong evidence to suggest that the toxicity of melamine and cyanurate is synergistic (see repeat dose toxicity section). Based on these relatively new data, the U.S. FDA applied an additional 10-fold safety

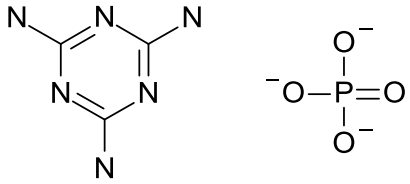
[23] A moiety is a discrete chemical entity that is a constituent part or component of a substance. A moiety of concern is often the parent substance itself for organic compounds. For inorganic compounds, the moiety of concern is typically a dissociated component of the substance or a transformation product.

factor to yield a combined safety factor of 1000-fold. Therefore, a TDI of 0.063 mg/kg bw/day was proposed (U.S. FDA 2008).

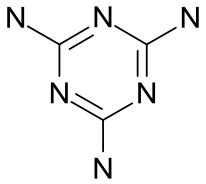
Melamine is degraded by three successive deamination reactions to ammeline (4,6-diamino-2-hydroxy-1,3,5-triazine), ammelide (6-amino-2,4- dihydroxy-1,3,5-triazine) and cyanuric acid(s- triazine-2,4,6-triol).

Melamine and phosphate are the expected breakdown products of melamine phosphate in the environment. The following chemical screen primarily uses toxicity data on melamine when the database for melamine phosphate is absent. Phosphate ion is also evaluated with regard to environmental parameters, but is not included in the human health analysis, as it is not expected to pose a risk to humans (U.S. EPA 1993).

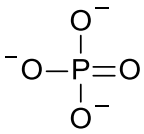
Chemical Structure of Surrogate:



Melamine phosphate (CAS #41583-09-9)



Melamine (CAS #108-78-1)



Phosphate (CAS #14265-44-2)

Human Health – Tier 1

Carcinogenicity (C) Score (H, M or L): *M*
Because no relevant carcinogenicity data for melamine polyphosphate were identified, the structurally similar melamine was used as a surrogate. Melamine polyphosphate was assigned a score of Moderate for carcinogenicity due to the conflicting evidence of carcinogenic properties for the surrogate, melamine, which induced bladder carcinomas in several animal studies.

***Note**: Unless specifically noted, information regarding animal strain or sex, dose, route of exposure, duration of experiment, or if these studies followed GLP guidelines was not provided by the authors of these studies.

Melamine polyphosphate

- Melamine polyphosphate is not listed as a known carcinogen by IARC, NTP, U.S. EPA, or CA Prop 65.

Melamine

- Significant formation of transitional cell carcinomas in the urinary bladder of male rats and significant chronic inflammation in the kidney of dosed female rats were observed. Carcinoma formation was significantly correlated with the incidence of bladder stones. A transitional-cell papilloma was observed in the urinary bladder of a single high dose male rat, and compound related lesions were observed in the urinary tract of dosed animals. Based on the mechanical nature of tumor formation, FDA and EPA considered melamine noncarcinogenic (U.S. EPA 2008).
- Increased incidence of acute and chronic inflammation and epithelial hyperplasia of the urinary bladder was observed in male mice. Bladder stones and compound related lesions were observed in the urinary tract of test animals. Melamine was not considered carcinogenic. No information concerning dose, route of administration, or other study details were provided (U.S. EPA 2008).
- Melamine-induced proliferative lesions of the rat urinary tract were directly due to the irritative stimulation of calculi, and not to molecular interactions between melamine or its metabolites with the bladder epithelium (U.S. EPA 2008).
- Water intake, used as an index of urinary output, was increased by NaCl treatment. Calculus formation resulting from melamine administration was suppressed dose-dependently by the simultaneous NaCl treatment. The main constituents of calculi were melamine and uric acid (total contents 61.1– 81.2%). The results indicate that melamine-induced proliferative lesions of the urinary tract of rats were directly due to the irritative stimulation of calculi, and not molecular interactions between melamine itself or its metabolites with the bladder epithelium (U.S. EPA 2008).
- As an initiator, melamine caused no significant increase in papillomas per mouse when compared to controls (U.S. EPA 2008).
- Diffuse papillary hyperplasia of the bladder epithelium and bladder calculi were observed in all melamine treated rats. Elevated spermidine/spermine N1-acetyltransferase (SAT) activity following melamine treatment was considered to be an indicator of cell proliferation (U.S. EPA 2008).
- Bladder tumors were only observed in the male rat and not in female rats or mice of either sex. An experiment did not reveal melamine as a tumor initiator. The formation of bladder stones and subsequent irritation of the bladder epithelium are necessary for tumor induction. Melamine is only indirectly responsible for the occurrence of bladder tumors. The incidence of calculi is dose dependent. The mechanism for tumor production is a non-genotoxic one. A threshold of 126 mg/kg for the formation of neoplasms can therefore be established. This value is based on a 2-year NTP feeding study with male Fisher 344 rats. The toxicity potential of melamine itself is considered low by the Consumer Product Safety Commission (Thomas and Brundage 2004).

Mutagenicity (M) and Genotoxicity Score (H, M or L): *M*

Because no relevant mutagenicity or genotoxicity data for melamine polyphosphate were identified, the structurally similar melamine was used as a surrogate. Melamine polyphosphate was assigned a score of Moderate for mutagenicity and genotoxicity due to the conflicting evidence of genotoxic properties for the surrogate, melamine, which induced chromosomal damage in several animal studies.

***Note**: Unless specifically noted, information regarding animal strain or sex, dose, route of exposure, duration of experiment, or if these studies followed GLP guidelines was not provided by the authors of these studies.

Melamine

- Bacterial forward mutation assay: Negative with and without liver activation (U.S. EPA 2008).
- *In vitro* mouse lymphoma test: Negative with and without liver activation (U.S. EPA 2008).
- *In vivo* mouse micronucleus test: The initial test gave a positive trend (P=0.003) for chromosomal damage; however, both peripheral blood smears and the repeat bone marrow test were negative. The overall conclusion was that melamine does not induce chromosomal damage (U.S. EPA 2008).
- *In vitro* chromosomal aberrations test: Negative in Chinese hamster ovary cells (CHO) with and without liver activation (U.S. EPA 2008).
- *In vitro* sister chromatid exchange assay: Negative in Chinese hamster ovary cells (CHO) with and without liver activation (U.S. EPA 2008).
- *In vivo* chromosome aberrations test in mice: Positive (U.S. EPA 2008).
- *In vivo* sister chromatid exchange assay in mice: Positive (U.S. EPA 2008)
- SOS/*umu* test: Negative for its ability to result in DNA damage and induce the expression of the *umu* operon (U.S. EPA 2008)
- Sex-linked recessive lethal/reciprocal translocation: Results were considered equivocal based on 0.18% and 0.36% total lethals following oral and injection exposure, respectively, compared to control total lethals of 0.07% for oral and 0.09% for injection (U.S. EPA 2008).
- *In vitro* flow cytometric (FCM) DNA repair assay: Negative for genotoxic effects (U.S. EPA 2008).
- Microscreen assay: Positive for genetic toxicity in *E. coli* WP2 uvrA assay (U.S. EPA 2008).

Reproductive (R) and Developmental (D) Toxicity Score (H, M or L): *L*

Because no relevant reproductive or developmental toxicity data were identified for melamine polyphosphate, the structurally similar melamine was used as a surrogate. Melamine polyphosphate was assigned a score of Low for reproductive and developmental toxicity because no basis of concern was identified.

***Note**: Unless specifically noted, information regarding animal strain or sex, dose, route of exposure, duration of experiment, or if these studies followed GLP guidelines was not provided by the authors of these studies.

Melamine

- Reproductive dysfunction was observed at 0.5 mg/m^3 and included effects on spermatogenesis (genetic material, sperm morphology, motility, and count), effects on the embryo/fetus (fetal death), preimplantation mortality (reduction in the number of implants per female), and total number of implants per corpora lutea (U.S EPA 2008).
- Mammary glands, ovaries, prostate, seminal vesicles, testes and uterus were examined macroscopically and microscopically in 13-week and in chronic toxicity studies with rats and mice and were found to be unaffected by melamine at each of the doses used. The lowest NOEL for systemic toxicity in these studies was 63 mg/kg/day (UNEP 1998).
- Melamine was not teratogenic in an investigation with rats. The NOEL for the fetuses was 1060 mg/kg/day, the highest dose tested. A maternal NOEL of 400 mg/kg/day was established based on decreased body weight and feed consumption and hematuria (UNEP 1998).

Endocrine Disruption (ED) Score (H, M or L): nd

- Melamine polyphosphate is not listed as a potential endocrine disruptor on the EU Priority List of Suspected Endocrine Disruptors.
- Melamine polyphosphate is not listed as a potential endocrine disruptor on the OSPAR List of Chemicals of Possible Concern.
- Melamine polyphosphate is not listed as a potential endocrine disruptor on the Red List of Chemicals (CPA 2009).

Neurotoxicity (N) Score (H, M or L): nd

- Melamine polyphosphate is not classified as a developmental neurotoxicant (Grandjean and Landrigan 2006).
- Melamine polyphosphate is not listed as a potential neurotoxicant on the Red List of Chemicals (CPA 2009).

Human Health – Tier 2

Acute Mammalian (AT) Toxicity Score (H, M or L): L

Melamine polyphosphate was assigned a score of Low for acute mammalian toxicity based on oral and dermal LD_{50} values of 2,000 or less mg/kg-bw from analog data. Data is from three different chemicals using two different routes of exposure in three different species of animals.

Melamine polyphosphate

- *Oral*: An LD_{50} of > 2,000 mg/kg was determined in the rat (U.S. EPA 2008).

Melamine phosphate

- *Oral*: An LD_{50} of > 2,000 mg/kg was determined in the mouse (Ciba 2005).
- *Dermal*: An LD_{50} of > 2,000 mg/kg was determined in the rabbit (Hummel Croton 2009).

Melamine

- *Oral*: An LD_{50} of 3,161 mg/kg (male) and 3,828 mg/kg (female) was determined in the rat (U.S. EPA 2008).
- *Oral*: An LD_{50} of > 6,400 mg/kg-bw was determined in the rat (U.S. EPA 2008).
- *Oral*: An LD_{50} of 3,296 mg/kg (male) and 7,014 mg/kg (female) was determined in the mouse (U.S. EPA 2008).
- *Oral*: An LD_{50} of 4,550 mg/kg was determined in the mouse (U.S. EPA 2008).
- *Dermal*: An LD_{50} of > 1,000 mg/kg was determined in the rabbit (U.S. EPA 2008).

Corrosion/ Irritation (Skin/ Eye) (Cr) Score (H, M or L): L
Melamine polyphosphate was assigned a score of Low for corrosion and irritation because no cause for concern was identified.

Melamine polyphosphate

- *Dermal*: Melamine polyphosphate was not irritating (no other data provided) (U.S. EPA 2008).
- *Ocular*: Melamine polyphosphate was slightly irritating (no other data provided) (U.S. EPA 2008).

Sensitization (Sn) Score (Skin and Respiratory) (H, M or L): *L*
Because no relevant sensitization data for melamine polyphosphate were identified, the structurally similar melamine phosphate and melamine were used as surrogates. Melamine polyphosphate was assigned a score of Low for sensitization because no basis for concern was identified.

Melamine Phosphate

- Melamine phosphate was not sensitizing in guinea pigs under Test Method OECD 406 (Ciba 2005).

Melamine

- Melamine was not sensitizing in human or guinea pig repeat insult patch test (UNEP 1998).

Systemic/ Organ (ST) Toxicity Score (includes organ effects and immunotoxicity) (H, M or L): *H*
Because no relevant systemic/organ toxicity data for melamine polyphosphate were identified, the structurally similar melamine was used as a surrogate. Melamine polyphosphate was assigned a score of High for systemic/organ toxicity based on analog data suggesting melamine causes kidney and bladder toxicity in animals.
***Note**: Unless specifically noted, information regarding animal strain or sex, dose, route of exposure, duration of experiment, or if these studies followed GLP guidelines was not provided by the authors of these studies.

Melamine

- Clinical signs observed during a 28-day repeat-dose study in rats included a dose-related increase in pilo-erection, lethargy, bloody urine spots in the cage and on the pelage of animals, and chromodacryorrhea. The incidence of urinary bladder calculi and urinary bladder hyperplasia in treated animals was dose dependant, with a significant relationship between the calculi and hyperplasia. Calculi composition indicated the presence of an organic matrix containing melamine,

phosphorus, sulfur, potassium, and chloride. Crystals of dimelamine monophosphate were identified in the urine. The NOAEL was estimated to be 2000 ppm (240 mg/kg/day), excluding the observed increase in water consumption and the incidence of crystalluria. The LOAEL was determined to be 4,000 ppm (475 mg/kg/day) based on the formation of calculus (U.S. EPA 2008).

- Following a 90-day repeat-dose study in rats, one male rat receiving 18000 ppm and two males receiving 6,000 ppm died. Mean body weight gain and feed consumption were reduced. Stones and diffuse epithelial hyperplasia in the urinary bladders were observed. Focal epithelial hyperplasia was observed in only 1 male. A second and third 13-week repeated dose toxicity study was conducted in rats at a dose range of 750 to 18000 ppm in order to determine the No Observed Adverse Effect Level; however, bladder stones were observed at all dose levels. At 18000 ppm, stones occurred in diets with and without the addition of ammonium chloride (U.S. EPA 2008).
- A single female mouse died after receiving 9000 ppm in a 90-day repeat-dose study. Mean body weight gain relative to controls was depressed. The incidence of mice with bladder stones was dose-related and was greater in males than in females. Sixty percent of mice having bladder ulcers also had urinary bladder stones. Bladder ulcers were multifocal or associated with inflammation (cystitis). Epithelial hyperplasia and bladder stones were observed together in 2 mice. Also, epithelial cell atypia was seen. No observed adverse effects were noted at 6000 ppm (U.S. EPA 2008).
- Following the incidence of melamine contamination in pet food, a pilot study was carried out in which cats (one per dose) were fed melamine, cyanuric acid, or a combination of both. For the melamine only group, one cat was fed 0.5% (181 mg/kg/day) and one cat, 1% (44-121 mg/kg/day) of the chemical for 11 days. In the cyuranic acid only group, one cat was fed 0.2% (49 mg/kg/day) for 4 days, 0.5% (121 mg/kg/day) for 3 days, and then 1% (243 mg/kg/day) for 3 days. In the final group, one cat received 32 mg/kg of each compound, one cat received 121 mg/kg of each compound, and one cat received 181 mg/kg of each compound for one day. On the second day, cats ate nothing or very little. The estimated doses were 2 mg/kg, 10 mg/kg, or 54 mg/kg of each compound. Cats dosed with a combination experienced acute renal failure and had to be euthanized after 48 hours. Findings included amorphous, rounded and fan-shaped crystals in the urine, and histologic lesions in the kidneys, the severity of which corresponded to the dose[24]. No effect on any renal parameter was observed in cats fed melamine or cyanuric acid alone (Puschner 2007).
- 400 mg/kg of either melamine or cyanuric acid or melamine and cyanuric acid was fed daily for 3 days to 75 fish, 4 pigs, and 1 cat. Animals were euthanized 1, 3, 6, 10, or 14 days later. All animals fed the combination of melamine and cyanuric acid developed renal crystals arranged in radial spheres. Melamine and cyanuric acid residues were identified in edible tissues of fish (Reimschuessel 2008).

Ecotoxicity

[24] The GHS category for toxic effects produced from a single exposure at $\leq$ 300 mg/kg/day or from multiple exposures at $\leq$ 2000 mg/kg/day is category 1.

Acute Aquatic (AA) Toxicity Score (H, M or L): *L*

Because no relevant acute aquatic toxicity data were identified for melamine polyphosphate and EPI Suite did not produce any results for ecotoxocity data, the structurally similar melamine phosphate, melamine, and phosphate were used as surrogates. Melamine polyphosphate was assigned a score of Low for acute aquatic toxicity based on L/EC_{50} values of 100 mg/L or greater.

Melamine Phosphate

- An LC_{50} of 100 mg/L was identified in a freshwater fish species (96 hour) (Ciba 2005).
- An EC_{50} of > 100 mg/L was identified *Daphnia magna* (aquatic invertebrate, 48 hour) (Ciba 2005).

Melamine

- An LC_{50} of > 500 mg/L was identified in *Leuciscus idus melanotus* (freshwater fish, 96 hour) (U.S. EPA 2008).
- An LC_{50} of > 3,000 mg/L was identified in *Poecilia reticulate* (freshwater fish, 96 hour) (UNEP 1998).
- An LC_{50} of > 2,000 mg/L was identified in *Daphnia magna* (aquatic invertebrate, 48 hour) (U.S. EPA 2008).
- An EC_{50} of > 2,000 mg/L was identified in *Daphnia magna* (aquatic invertebrate, 48 hour) (UNEP 1998).
- An EC_{50} of 940 mg/L was identified in *Scenedesmus pannonicus* (green algae, 96 hour) (U.S. EPA 2008).

Phosphate

- This chemical is designated to the ECOSAR class neutral organics. The most conservative estimated L/EC_{50} acute values for fish (96-hr), daphnid (48-hr), and green algae (96-hr) are >100 mg/L (U.S. EPA 2009).

Chronic Aquatic (CA) Toxicity Score (H, M or L): *L*

Because no chronic aquatic toxicity data were identified for melamine polyphosphate and EPI Suite did not produce any results for ecotoxocity data, the structurally similar melamine and phosphate were used as surrogates. Melamine polyphosphate was assigned a score of Low for chronic aquatic toxicity based on NOEC values greater than 10 mg/L.

Melamine

- An NOEC of 1,000 mg/L was identified in *Jordanella floridae* (freshwater fish, 35 day) (U.S. EPA 2008).
- An NOEC of < 125 to > 1,000 mg/L was identified in a freshwater fish species (UNEP 1998).
- An LC_{50} of 32-56 mg/L was identified in *Daphnia magna* (aquatic invertebrate, 21 day) (U.S. EPA 2008).
- An LC_{50} of > 32 mg/L was identified in *Daphnia magna* (aquatic invertebrate, 21 day) (UNEP 1998).
- An NOEC of 18 mg/L was identified in *Daphnia magna* (aquatic invertebrate, 21 day) (UNEP 1998).

- An EC_{50} of 1,680 mg/L was identified in an aquatic plant species (14 day) (UNEP 1998).

Phosphate

- This chemical is designated to the ECOSAR class neutral organics. The most conservative estimated L/EC_{50} chronic values for fish (30-day), daphnid (duration not given), and green algae (duration not given) are >100 mg/L (U.S. EPA 2009).

Environmental Fate

Persistence (P) Score (vH, H, M, or L): *M*

Because no relevant persistence data for melamine polyphosphate were identified, the structurally similar melamine phosphate, melamine, and phosphate were used as surrogates. Melamine polyphosphate was assigned as score of Moderate for persistence based on analog data suggesting melamine polyphosphate will not biodegrade rapidly.

Melamine polyphosphate

- Based on evidence from melamine, melamine polyphosphate is expected to show moderate persistence and will not biodegrade rapidly (U.S. EPA 2008)

Melamine phosphate

- EPI Suite was unable to predict the environmental fate of melamine phosphate. Because it is a salt, it is expected to dissociate readily in the environment. Therefore, it is appropriate to evaluate the persistence of the two component ions instead.
- Above ~200°C melamine phosphate will react to melamine pyro-phosphate with release of reaction water, which will result in a heat sink. Above ~260°C melamine-pyrophosphate will react under release of reaction water to melamine-polyphosphates which again results in a heat sink effect. Above 350°C, melamine-polyphosphate undergoes endothermic decomposition and releases phosphoric acid (Ciba 2005).

Melamine

- A standard 5-day biochemical oxygen demand (BOD) test indicated melamine was not biodegradable (Saski 1970).
- Pure culture studies of *Pseudomonas* strain A exposed to 3mM melamine indicated that melamine is degraded to ammeline and eventually cyanuric acid (Jutzi 1982).
- Water is the most relevant compartment in the environmental fate of the substance (UNEP 1998).
- In water, melamine is expected to adsorb to sediment at acidic pHs (Weber 1970).
- Melamine is not expected to undergo hydrolysis in the environment due to the lack of functional groups that hydrolyze under environmental conditions (Lyman 1990).
- Melamine can be hydrolyzed by mineral acid or inorganic alkali (Crews 2005).

Phosphate

- The phosphate anion is expected to adsorb strongly to soil or colloidal particles in the water column. Salts of phosphoric acid generally dissociate (U.S EPA 1993).

Bioaccumulation (B) Score (vH, H, M, or L): L
Melamine polyphosphate was assigned a score of Low for bioaccumulation based on professional opinion and analog data that suggests the chemical will not bioaccumulate.

Melamine polyphosphate

- Because of its high water solubility (20g/L), the bioconcentration factor (BCF) is expected to be <1,000 (U.S. EPA 2008).

Melamine

- The bioaccumulation potential of melamine is low. No remarkable contribution of food from aquatic organisms to the uptake of melamine in humans is therefore expected (UNEP 1998).

Phosphate

- BCFBAF predicts a bioconcentration factor (BCF) of 3.16 for phosphate (U.S. EPA 2010)

Physical Properties

Explosivity (Ex) Hazard Rating (H, M or L): L
Melamine polyphosphate was assigned a score of Low for reactivity because no basis for concern was identified.

- Melamine polyphosphate is not explosive (U.S. EPA 2008).

Flammability (F) Hazard Rating (H, M or L): L
Melamine polyphosphate was assigned a score of Low for flammability because no basis for concern was identified.

- Melamine polyphosphate is not flammable (U.S. EPA 2008).

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EPI Suite Results for Melamine:

CAS Number: 108-78-1
SMILES : n(c(nc(n1)N)N)c1N
CHEM : 1,3,5-Triazine-2,4,6-triamine
MOL FOR: C3 H6 N6
MOL WT : 126.12
---------- EPI SUMMARY (v4.00) ----------
Physical Property Inputs:
Log Kow (octanol-water): ------
Boiling Point (deg C) : ------
Melting Point (deg C) : ------
Vapor Pressure (mm Hg) : ------
Water Solubility (mg/L): ------
Henry LC (atm-m3/mole) : ------

Log Octanol-Water Partition Coef (SRC):
Log Kow (KOWWIN v1.67 estimate) = -0.38
Log Kow (Exper. database match) = -1.37
Exper. Ref: HANSCH,C ET AL. (1995)

Boiling Pt, Melting Pt, Vapor Pressure Estimations (MPBPVP v1.43):
Boiling Pt (deg C): 329.78 (Adapted Stein & Brown method)
Melting Pt (deg C): 133.08 (Mean or Weighted MP)
VP(mm Hg,25 deg C): 8.93E-008 (Modified Grain method)
VP (Pa, 25 deg C) : 1.19E-005 (Modified Grain method)
MP (exp database): 345 dec deg C
VP (exp database): 3.59E-10 mm Hg (4.79E-008 Pa) at 20 deg C
Subcooled liquid VP: 5.25E-007 mm Hg (20 deg C, exp database VP)
: 7E-005 Pa (20 deg C, exp database VP)

Water Solubility Estimate from Log Kow (WSKOW v1.41):
Water Solubility at 25 deg C (mg/L): 1e+006
log Kow used: -1.37 (expkow database)
no-melting pt equation used
Water Sol (Exper. database match) = 3230 mg/L (20 deg C)
Exper. Ref: YALKOWSKY,SH & HE,Y (2003)

Water Sol Estimate from Fragments:
Wat Sol (v1.01 est) = 1040.5 mg/L

ECOSAR Class Program (ECOSAR v1.00):
Class(es) found:
Anilines (amino-meta)
Triazines
Melamines

Henrys Law Constant (25 deg C) [HENRYWIN v3.20]:
Bond Method : 1.89E-013 atm-m3/mole (1.92E-008 Pa-m3/mole)
Group Method: Incomplete
Exper Database: 1.84E-14 atm-m3/mole (1.86E-009 Pa-m3/mole)
For Henry LC Comparison Purposes:
User-Entered Henry LC: not entered
Henrys LC [via VP/WSol estimate using User-Entered or Estimated values]:
HLC: 1.482E-014 atm-m3/mole (1.502E-009 Pa-m3/mole)
VP: 8.93E-008 mm Hg (source: MPBPVP)

WS: 1E+006 mg/L (source: WSKOWWIN)

Log Octanol-Air Partition Coefficient (25 deg C) [KOAWIN v1.10]:
Log Kow used: -1.37 (exp database)
Log Kaw used: -12.124 (exp database)
Log Koa (KOAWIN v1.10 estimate): 10.754
Log Koa (experimental database): None

Probability of Rapid Biodegradation (BIOWIN v4.10):
Biowin1 (Linear Model) : -0.0042
Biowin2 (Non-Linear Model) : 0.0000
Expert Survey Biodegradation Results:
Biowin3 (Ultimate Survey Model): 2.2697 (weeks-months)
Biowin4 (Primary Survey Model) : 3.2831 (days-weeks)
MITI Biodegradation Probability:
Biowin5 (MITI Linear Model) : -0.0193
Biowin6 (MITI Non-Linear Model): 0.0000
Anaerobic Biodegradation Probability:
Biowin7 (Anaerobic Linear Model): -0.0756
Ready Biodegradability Prediction: NO

Hydrocarbon Biodegradation (BioHCwin v1.01):
Structure incompatible with current estimation method!

Sorption to aerosols (25 Dec C)[AEROWIN v1.00]:
Vapor pressure (liquid/subcooled): 7E-005 Pa (5.25E-007 mm Hg)
Log Koa (Koawin est): 10.754
Kp (particle/gas partition coef. (m3/ug)):
Mackay model : 0.0429
Octanol/air (Koa) model: 0.0139
Fraction sorbed to airborne particulates (phi):
Junge-Pankow model : 0.608
Mackay model : 0.774
Octanol/air (Koa) model: 0.527

Atmospheric Oxidation (25 deg C) [AopWin v1.92]:
Hydroxyl Radicals Reaction:
OVERALL OH Rate Constant = 0.6596 E-12 cm3/molecule-sec
Half-Life = 16.216 Days (12-hr day; 1.5E6 OH/cm3)
Ozone Reaction:
No Ozone Reaction Estimation
Fraction sorbed to airborne particulates (phi):
0.691 (Junge-Pankow, Mackay avg)
0.527 (Koa method)
Note: the sorbed fraction may be resistant to atmospheric oxidation

Soil Adsorption Coefficient (KOCWIN v2.00):
Koc : 32.28 L/kg (MCI method)
Log Koc: 1.509 (MCI method)
Koc : 1 L/kg (Kow method)
Log Koc: 0.000 (Kow method)

Aqueous Base/Acid-Catalyzed Hydrolysis (25 deg C) [HYDROWIN v2.00]:
Rate constants can NOT be estimated for this structure!

Bioaccumulation Estimates (BCFBAF v3.00):
Log BCF from regression-based method = 0.500 (BCF = 3.162 L/kg wet-wt)

Log Biotransformation Half-life (HL) = -3.1607 days (HL = 0.0006907 days)
Log BCF Arnot-Gobas method (upper trophic) = -0.049 (BCF = 0.8938)
Log BAF Arnot-Gobas method (upper trophic) = -0.049 (BAF = 0.8938)
log Kow used: -1.37 (expkow database)

Volatilization from Water:
Henry LC: 1.84E-014 atm-m3/mole (Henry experimental database)
Half-Life from Model River: 3.573E+010 hours (1.489E+009 days)
Half-Life from Model Lake : 3.898E+011 hours (1.624E+010 days)

Removal In Wastewater Treatment:
Total removal: 1.85 percent
Total biodegradation: 0.09 percent
Total sludge adsorption: 1.75 percent
Total to Air: 0.00 percent
(using 10000 hr Bio P,A,S)

Removal In Wastewater Treatment:
Total removal: 21.97 percent
Total biodegradation: 20.53 percent
Total sludge adsorption: 1.44 percent
Total to Air: 0.00 percent
(using Biowin/EPA draft method)

Level III Fugacity Model:

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	3.41e-007	389	1000
Water	25	900	1000
Soil	74.9	1.8e+003	1000
Sediment	0.086	8.1e+003	0

Persistence Time: 1.37e+003 hr

ECOSAR Results for Melamine:

SMILES : n(c(nc(n1)N)N)c1N
CHEM : 1,3,5-Triazine-2,4,6-triamine
CAS Num: 000108-78-1
ChemID1:
ChemID2:
ChemID3:
MOL FOR: C3 H6 N6
MOL WT : 126.12
Log Kow: -0.38 (KowWin estimate)
Melt Pt:
Wat Sol: 3230 mg/L (experimental database)

ECOSAR v1.00 Class(es) Found

Anilines (amino-meta)
Triazines
Melamines

ECOSAR Class	Organism	Predicted Duration	End Pt	mg/L (ppm)
Anilines (amino-meta)	: Fish	96-hr	LC50	1863.183

Anilines (amino-meta) : Daphnid 48-hr LC50 6.837
Anilines (amino-meta) : Green Algae 96-hr EC50 2.789
Anilines (amino-meta) : Fish ChV 186.204 !
Anilines (amino-meta) : Daphnid ChV 0.069
Anilines (amino-meta) : Green Algae ChV 0.054 !

Triazines : Fish 96-hr LC50 42792.074 *
Triazines : Daphnid 48-hr LC50 4418.740 *
Triazines : Green Algae 96-hr EC50 276.519
Triazines : Fish ChV 1007.473 !
Triazines : Daphnid 21-day ChV 150.580
Triazines : Green Algae ChV 39.539

Melamines : Fish 96-hr LC50 390.882
Melamines : Daphnid 48-hr LC50 274.094
Melamines : Green Algae 96-hr EC50 324.968
Melamines : Fish ChV 1102.529
Melamines : Daphnid ChV 16.591 !
Melamines : Green Algae ChV 81.248 !

Neutral Organic SAR (Baseline Toxicity)	: Fish	96-hr	LC50	10068.581 *
	: Daphnid	48-hr	LC50	4356.359 *
	: Green Algae	96-hr	EC50	706.784
	: Fish	ChV		1007.473
	: Daphnid	ChV		264.059
	: Green Algae	ChV		165.581

Note: * = asterisk designates: Chemical may not be soluble enough to measure this predicted effect.

Note: ! = exclamation designates: The toxicity value was determined from a predicted SAR using established acute-to-chronic ratios and ECOSAR regression techniques which are documented in the supporting Technical Reference Manual. When possible, this toxicity value should be considered in a weight of evidence approach.

Anilines (amino-meta):

For Fish and Daphnid Acute Toxicity Values: If the log Kow of the chemical is greater than 5.0, or if the compound is solid and the LC50 exceeds the water solubility by 10X, no effects at saturation are predicted for these endpoints.

For Green Algae Acute Toxicity Values: If the log Kow of the chemical is greater than 6.4, or if the compound is solid and the EC50 exceeds the water solubility by 10X, no effects at saturation are predicted for these endpoints.

For All Chronic Toxicity Values: If the log Kow of the chemical is greater than 8.0, or if the compound is solid and the ChV exceeds the water solubility by 10X, no effects at saturation are predicted for these endpoints.

ECOSAR v1.00 SAR Limitations:

Maximum LogKow: 5.0 (LC50)
Maximum LogKow: 6.4 (EC50)
Maximum LogKow: 8.0 (ChV)
Maximum Mol Wt: 1000

Triazines:

For Fish and Daphnid Acute Toxicity Values: If the log Kow of the chemical is greater than 5.0, or if the compound is solid and the LC50 exceeds the water solubility by 10X, no effects at saturation are predicted for these endpoints.

For Green Algae Acute Toxicity Values: If the log Kow of the chemical is greater than 6.4, or if the compound is solid and the EC50 exceeds the water solubility by 10X, no effects at saturation are predicted for these endpoints.

For All Chronic Toxicity Values: If the log Kow of the chemical is greater than 8.0, or if the compound is solid and the ChV exceeds the water solubility by 10X, no effects at saturation are predicted for these endpoints.

ECOSAR v1.00 SAR Limitations:

Maximum LogKow: 5.0 (LC50)
Maximum LogKow: 6.4 (EC50)
Maximum LogKow: 8.0 (ChV)
Maximum Mol Wt: 1000

Melamines :

For Fish and Daphnid Acute Toxicity Values: If the log Kow of the chemical is greater than 5.0, or if the compound is solid and the LC50 exceeds the water solubility by 10X, no effects at saturation are predicted for these endpoints.

For Green Algae Acute Toxicity Values: If the log Kow of the chemical is greater than 6.4, or if the compound is solid and the EC50 exceeds the water solubility by 10X, no effects at saturation are predicted for these endpoints.

For All Chronic Toxicity Values: If the log Kow of the chemical is greater than 8.0, or if the compound is solid and the ChV exceeds the water solubility by 10X, no effects at saturation are predicted for these endpoints.

ECOSAR v1.00 SAR Limitations:

Maximum LogKow: 5.0 (LC50)
Maximum LogKow: 6.4 (EC50)
Maximum LogKow: 8.0 (ChV)
Maximum Mol Wt: 1000

Baseline Toxicity SAR Limitations:

Maximum LogKow: 5.0 (Fish 96-hr LC50; Daphnid LC50)
Maximum LogKow: 6.4 (Green Algae EC50)
Maximum LogKow: 8.0 (ChV)
Maximum Mol Wt: 1000

EPI Suite Results for Phosphate:

CAS Number: 14265-44-2
SMILES : OP(=O)(O)O
CHEM : PHOSPHATE
MOL FOR: H3 O4 P1

MOL WT : 98.00
---------- EPI SUMMARY (v4.00) ----------
Physical Property Inputs:
Log Kow (octanol-water): ------
Boiling Point (deg C) : ------
Melting Point (deg C) : ------
Vapor Pressure (mm Hg) : ------
Water Solubility (mg/L): ------
Henry LC (atm-m3/mole) : ------

Log Octanol-Water Partition Coef (SRC):
*** WARNING: Inorganic Compound (Outside Estimation Domain)
Log Kow (KOWWIN v1.67 estimate) = -0.77

Boiling Pt, Melting Pt, Vapor Pressure Estimations (MPBPVP v1.43):
*** WARNING: Inorganic Compound (Outside Estimate Domain) ***
*** WARNING: Estimations NOT VALID ***
Boiling Pt (deg C): 480.00 (Adapted Stein & Brown method)
Melting Pt (deg C): 90.27 (Mean or Weighted MP)
VP(mm Hg,25 deg C): 6.09E-011 (Modified Grain method)
VP (Pa, 25 deg C) : 8.12E-009 (Modified Grain method)
MP (exp database): 42.35 deg C
Subcooled liquid VP: 8.76E-011 mm Hg (25 deg C, Mod-Grain method)
: 1.17E-008 Pa (25 deg C, Mod-Grain method)

Water Solubility Estimate from Log Kow (WSKOW v1.41):
*** WARNING: Inorganic Compound (Outside Estimation Domain)**
Water Solubility at 25 deg C (mg/L): 5.386e+005
log Kow used: -0.77 (estimated) no-melting pt equation used

Water Sol Estimate from Fragments:
*** WARNING: Inorganic Compound (Outside Estimation Domain)***
*** WARNING: Wat Sol Estimation NOT Valid ***
Wat Sol (v1.01 est) = 1e+006 mg/L

ECOSAR Class Program (ECOSAR v1.00):
Class(es) found:
Neutral Organics

Henrys Law Constant (25 deg C) [HENRYWIN v3.20]:
*** WARNING: Inorganic Compound (Outside Estimation Domain) **
*** WARNING: Estimation NOT VALID **
Bond Method : 7.60E-015 atm-m3/mole (7.70E-010 Pa-m3/mole)
Group Method: Incomplete
For Henry LC Comparison Purposes:
User-Entered Henry LC: not entered
Henrys LC [via VP/WSol estimate using User-Entered or Estimated values]:
HLC: 1.458E-017 atm-m3/mole (1.477E-012 Pa-m3/mole)
VP: 6.09E-011 mm Hg (source: MPBPVP)
WS: 5.39E+005 mg/L (source: WSKOWWIN)

Log Octanol-Air Partition Coefficient (25 deg C) [KOAWIN v1.10]:
*** WARNING: Inorganic Compound (Outside Estimation Domain)**
*** WARNING: Estimation NOT VALID ***
Log Kow used: -0.77 (KowWin est)
Log Kaw used: -12.508 (HenryWin est)
Log Koa (KOAWIN v1.10 estimate): 11.738

Log Koa (experimental database): None

Probability of Rapid Biodegradation (BIOWIN v4.10):
*** WARNING: Inorganic Compound (Outside Estimation Domain)**
*** WARNING: Estimation NOT VALID ***
Biowin1 (Linear Model) : 0.7009
Biowin2 (Non-Linear Model) : 0.8344
Expert Survey Biodegradation Results:
Biowin3 (Ultimate Survey Model): 2.9826 (weeks)
Biowin4 (Primary Survey Model) : 3.7064 (days-weeks)
MITI Biodegradation Probability:
Biowin5 (MITI Linear Model) : 0.4206
Biowin6 (MITI Non-Linear Model): 0.4247
Anaerobic Biodegradation Probability:
Biowin7 (Anaerobic Linear Model): 0.8361
Ready Biodegradability Prediction: NO

Hydrocarbon Biodegradation (BioHCwin v1.01):
Structure incompatible with current estimation method!

Sorption to aerosols (25 Dec C)[AEROWIN v1.00]:
Vapor pressure (liquid/subcooled): 1.17E-008 Pa (8.76E-011 mm Hg)
Log Koa (Koawin est): 11.738
Kp (particle/gas partition coef. (m3/ug)):
Mackay model : 257
Octanol/air (Koa) model: 0.134
Fraction sorbed to airborne particulates (phi):
Junge-Pankow model : 1
Mackay model : 1
Octanol/air (Koa) model: 0.915

Atmospheric Oxidation (25 deg C) [AopWin v1.92]:
*** WARNING: Inorganic Compound (Outside Estimation Domain)***
Hydroxyl Radicals Reaction:
OVERALL OH Rate Constant = 0.4200 E-12 cm3/molecule-sec
Half-Life = 25.467 Days (12-hr day; 1.5E6 OH/cm3)
Ozone Reaction:
No Ozone Reaction Estimation
Fraction sorbed to airborne particulates (phi):
1 (Junge-Pankow, Mackay avg)
0.915 (Koa method)
Note: the sorbed fraction may be resistant to atmospheric oxidation

Soil Adsorption Coefficient (KOCWIN v2.00):
*** WARNING: Inorganic Coumpound (Outside Estimation Domain) **
*** WARNING: Estimation NOT VALID **
Koc : 1.407 L/kg (MCI method)
Log Koc: 0.148 (MCI method)
Koc : 4.004 L/kg (Kow method)
Log Koc: 0.603 (Kow method)

Aqueous Base/Acid-Catalyzed Hydrolysis (25 deg C) [HYDROWIN v2.00]:
Rate constants can NOT be estimated for this structure!

Bioaccumulation Estimates (BCFBAF v3.00):
Log BCF from regression-based method = 0.500 (BCF = 3.162 L/kg wet-wt)
Log Biotransformation Half-life (HL) = -2.0250 days (HL = 0.009441 days)

Log BCF Arnot-Gobas method (upper trophic) = -0.047 (BCF = 0.898)
Log BAF Arnot-Gobas method (upper trophic) = -0.047 (BAF = 0.898)
log Kow used: -0.77 (estimated)

Volatilization from Water:
Henry LC: 7.6E-015 atm-m3/mole (estimated by Bond SAR Method)
Half-Life from Model River: 7.626E+010 hours (3.178E+009 days)
Half-Life from Model Lake : 8.32E+011 hours (3.466E+010 days)

Removal In Wastewater Treatment:
Total removal: 1.85 percent
Total biodegradation: 0.09 percent
Total sludge adsorption: 1.76 percent
Total to Air: 0.00 percent
(using 10000 hr Bio P,A,S)

Removal In Wastewater Treatment:
Total removal: 75.06 percent
Total biodegradation: 74.44 percent
Total sludge adsorption: 0.62 percent
Total to Air: 0.00 percent
(using Biowin/EPA draft method)

Level III Fugacity Model:

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	0.000587	611	1000
Water	37.3	360	1000
Soil	62.7	720	1000
Sediment	0.0704	3.24e+003	0

Persistence Time: 591 hr

ECOSAR Results for Phosphate:

SMILES : OP(=O)(O)O
CHEM : PHOSPHATE
CAS Num: 014265-44-2
ChemID1:
ChemID2:
ChemID3:
MOL FOR: H3 O4 P1
MOL WT : 98.00
Log Kow: -0.77 (KowWin estimate)
Melt Pt:
Wat Sol: 5.386E+005 mg/L (WskowWin estimate)

ECOSAR v1.00 Class(es) Found

Neutral Organics

ECOSAR Class	Organism	Predicted Duration	End Pt	mg/L (ppm)
Neutral Organics	: Fish	96-hr	LC50	20670.012
Neutral Organics	: Fish	14-day	LC50	19987.178
Neutral Organics	: Daphnid	48-hr	LC50	7739.504
Neutral Organics	: Green Algae	96-hr	EC50	1103.342

Neutral Organics	: Fish	30-day	ChV	1788.696
Neutral Organics	: Daphnid		ChV	578.554
Neutral Organics	: Green Algae		ChV	265.686
Neutral Organics	: Fish (SW)	96-hr	LC50	35468.875
Neutral Organics	: Mysid Shrimp	96-hr	LC50	1.49e+005
Neutral Organics	: Fish (SW)		ChV	612.736
Neutral Organics	: Mysid Shrimp (SW)		ChV	29203.973
Neutral Organics	: Earthworm	14-day	LC50	330.099

Note: * = asterisk designates: Chemical may not be soluble enough to measure this predicted effect.

Neutral Organics:

For Fish LC50 (96-h), Daphnid LC50, Mysid: If the log Kow is greater than 5.0, or if the compound is solid and the LC50 exceeds the water solubility by 10X, no effects at saturation are predicted.

For Fish LC50 (14-day) and Earthworm LC50: If the log Kow is greater than 6.0, or if the compound is solid and the LC50 exceeds the water solubility by 10X, no effects at saturation are predicted.

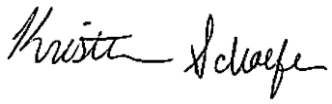
For Green Algae Acute Toxicity Values: If the log Kow of the chemical is greater than 6.4, or if the compound is solid and the EC50 exceeds the water solubility by 10X, no effects at saturation are predicted for these endpoints.

For All Chronic Toxicity Values: If the log Kow of the chemical is greater than 8.0, or if the compound is solid and the ChV exceeds the water solubility by 10X, no effects at saturation are predicted for these endpoints.

ECOSAR v1.00 SAR Limitations:

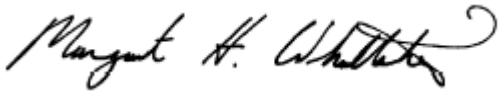
Maximum LogKow: 5.0 (Fish 96-hr LC50; Daphnid LC50, Mysid LC50)
Maximum LogKow: 6.0 (Fish 14-day LC50; Earthworm LC50)
Maximum LogKow: 6.4 (Green Algae EC50)
Maximum LogKow: 8.0 (ChV)
Maximum Mol Wt: 1000

Melamine Polyphosphate Green Screen Evaluation Prepared By:



Kristen M. Schaefer, M.F.S.
Associate Toxicologist
ToxServices LLC

Melamine Polyphosphate Green Screen Evaluation QC'd By:



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APPENDIX IX I: GREEN SCREEN FOR RED PHOSPHORUS (CAS #7723-14-0)[25]

Also Called: Amgard CPC, Amgard CPC 405, Black phosphorus, Bonide blue death rat killer, Caswell No. 663, Common sense cockroach and rat preparations, EINECS 231-768-7, EPA Pesticide Chemical Code 066502, Exolit 385, Exolit 405, Exolit LPKN, Exolit LPKN 275, Exolit RP 605, Exolit RP 650, Exolit RP 652, Exolit RP 654, Exolit VPK-n 361, FR-T 2 (element), Gelber phosphor, Gelber phosphor [German], HSDB 1169, Hishigado, Hishigado AP, Hishigado CP, Hishigado NP 10, Hishigado PL, Hostaflam RP 602, Hostaflam RP 614, Hostaflam RP 622, Hostaflam RP 654, Masteret 70450, NVE 140, Nova Sol R 20, Novaexcel 140, Novaexcel 150, Novaexcel F 5, Novaexcel ST 100, Novaexcel ST 140, Novaexcel ST 300, Novared 120UF, Novared 120UFA, Novared 120VFA, Novared 140, Novared 280, Novared C 120, Novared F 5, Phosphorus, Phosphorus (red), Phosphorus-31, Rat-Nip, Red phosphorus, UNII-27YLU75U4W, Violet phosphorus, White Phosphorus

Chemical Structure of Red Phosphorus:

P

For Inorganic Chemicals:
Define Form & Physiochemical Properties

13. Particle size (e.g. silica of respirable size) – unknown
14. Structure (e.g. amorphous vs. crystalline) – Crystalline (O'Neil 2001)
15. Mobility (e.g. Water solubility, volatility) – 2.4 mg/L at 15˚C; 4.1 mg/L at 25˚C (ESIS 2000)

Identify Applications/Functional Uses: Flame retardant

Green Screen Rating[26]: Red phosphorus was assigned a Green Screen Benchmark Score of 1 based on the High human acute toxicity (AT) and systemic toxicity (ST) as well as the High neurotoxicity (N), which is a priority effect (1d).

Green Screen (Version 1) Levels of Concern for Red Phosphorus														
Human – Tier 1					Human – Tier 2				Eco		Fate		Physical	
C	M	R/D	ED	N	AT	Cr	Sn	ST	AA	CA	P	B	Ex	F
L	L	L	nd	H	H	H	L	H	L	M	M	L	H	H

*Endpoints in italics were assigned using estimated values and professional judgment (Structure Activity Relationships).

[25] CPA recommends independent third-party validation of all Green Screen assessments. No independent third-party validation has been done for this assessment . Companies may not make marketing claims based on a Green Screen assessment that has not undergone an independent validation.

[26] For inorganic chemicals with low human and ecotoxicity across all hazard endpoints and low bioaccumulation, persistence alone will not be deemed problematic. Inorganic chemicals that are only persistent will be evaluated under the criteria for Benchmark 4.

Transformation Products and Ratings:
Identify relevant fate and transformation products (i.e., dissociation products, transformation products, valence states) and/or moieties of concern[27]

Life Cycle Stage	Transformation Pathway	Transformation Products	CAS #	Green Screen Rating
	Possible product of phosphorus coming in direct contact with air and water.	Phosphine	7803-51-2	Present on the Red List of Chemicals as a possible neurotoxicant (CPA 2009).
End of Life	Combustion	Phosphorus acids	10294-56-1 and 13598-36-2	Not present on the Red List of Chemicals (CPA 2009).
End of Life	Combustion	Polyphosphoric acids	8017-16-1	Not present on the Red List of Chemicals (CPA 2009).
End of Life	Decomposition	Phosphorus oxides	Multiple	Not present on the Red List of Chemicals (CPA 2009).
	Reaction with Water	Hypophosphrous acid	6303-21-5	Not present on the Red List of Chemicals (CPA 2009).
	Reaction with Water	Phosphoric acid	7664-38-2	Not present on the Red List of Chemicals (CPA 2009).

*The above transformation products were screened against the CPA's table of Red List chemicals.

Introduction

Phosphorus exists in three main alloptropic forms: white (sometimes called yellow phosphorus), black, and red (O'Neil 2001). Red phosphorus is a stable transformation form of the element phosphorus (Leisewitz 2000). Toxicity data for red phosphorus produced conflicting conclusions; not all studies stated specifically the allotrope of phosphorus being tested therefore the results varied widely. Red phosphorus is less toxic than the white allotrope however; most studies did not distinguish between the red and the white forms and only identified the compound as "phosphorus." In an effort to be conservative, all data, unless it specifically stated white phosphorus was used, was taken into consideration.

Red phosphorus is an additive flame retardant stabilized by wetting it with additives or by micro-encapsulation with phenol formaldehyde resins. Red phosphorus decomposes

[27] A moiety is a discrete chemical entity that is a constituent part or component of a substance. A moiety of concern is often the parent substance itself for organic compounds. For inorganic compounds, the moiety of concern is typically a dissociated component of the substance or a transformation product.

thermally above 400˚C. Its mode of action involves forming a rigid, glassy carbonized layer on the polymer that consists mainly of polyphosphoric acid, which prevents the re-supply of flammable material in the gas phase. The oxygen required for the formation of the polyphosphoric acid is derived preferentially from the matrix (polymer or other material). This makes red phosphorus a highly effective flame retardant in materials with high oxygen content such as cellulose or other oxygen-containing plastics. A synergist is required in oxygen-free materials such as polyolefins or polystyrene. Impurities found in red phosphorus mainly stem from white phosphorus which ignites in the presence of air (up to 200 mg/kg red phosphorus).

Red phosphorus does not dissolve easily in water (Leisewitz 2000). Risks of environmental contamination with red phosphorus as a result of its use as a flame retardant is low, while inertial and micro-encapsulated red phosphorus do not pose a hazard to the environment. Oral ingestion of free RP is unlikely due to its degradability in the environment. Fumes can lead to irritations of the skin and mucous membranes. Lack of oxygen can lead to the formation of white phosphorus, also called yellow phosphorus, which can ignite in the presence of air. The National Institute for Occupational Safety and Health (NIOSH) has assigned red phosphorus an exposure limit of 0.1 mg/m^3 (TWA) and an immediately dangerous to life or health value (IDLH) of 5 mg/m^3 (Avogadro 2000). OSHA assigned red phosphorus a Permissible Exposure Limit (PEL) of 0.1 mg/m^3 (Avogadro 2000).

Human Health – Tier 1

Carcinogenicity (C) Score: (H, M or L): L
Red phosphorus was assigned a score of Low for carcinogenicity because no basis for concern was identified.

- Red phosphorus is not listed as a known carcinogen by IARC, NTP, U.S. EPA, or CA Prop 65.

Mutagenicity (M) and Genotoxicity Score: (H, M or L): L
Red phosphorus was assigned a score of Low for mutagenicity and genotoxicity because data from animal studies suggests the chemical is not clastogenic.

- Female rats were exposed to red phosphorus/butyl rubber at 1,000 mg/m^3 over a 2 week period. It was concluded the test substance was a weak clastogen. No other details of the study were provided (U.S. EPA 2010b).

Reproductive (R) and Developmental (D) Toxicity Score: (H, M or L): L
Red phosphorus was assigned a score of Low for reproductive and developmental toxicity because no basis for concern was identified.

- There are no data to suggest that a single inhalation exposure to red phosphorus would cause developmental or reproductive toxicity (no other data provided) (U.S. EPA 2010b).

Endocrine Disruption (ED) Score: (H, M or L): nd

- Red phosphorus is not listed as a potential endocrine disruptor on the EU Priority List of Suspected Endocrine Disruptors.
- Red phosphorus is not listed as a potential endocrine disruptor on the OSPAR List of Chemicals of Possible Concern.
- Red phosphorus is not listed as a potential endocrine disruptor on the Red List of Chemicals (CPA 2009).

Neurotoxicity (N) Score: (H, M or L): H
Red phosphorus was assigned a score of High for neurotoxicity based on it being listed as a potential neurotoxicant.

- Red phosphorus is classified as a developmental neurotoxicant (Grandjean and Landrigan 2006).
- Red phosphorus is listed as a potential neurotoxicant on the Red List of Chemicals (CPA 2009).

Human Health – Tier 2

Acute Mammalian (AT) Toxicity Score: (H, M or L): H
Red phosphorus was assigned a score of High for acute mammalian toxicity based on oral LD_{50} values < 50 mg/kg-bw. Data is based on studies from two routes of exposure in four different species.
***Note:** Unless specifically noted, it is unclear if these LD_{50} values apply to the red phosphorus or the white (more toxic) phosphorus.

- *Oral*: An LD_{50} of 3.3 mg/kg was determined in the rat (Avogadro 2000).
- *Oral*: An LD_{50} of 11.5 mg/kg was determined in the rat (ChemCAS 2004).
- *Oral*: An LD_{50} of 4.8 mg/kg was determined in the mouse (Avogadro 2000).
- *Oral*: An LD_{50} of 11.5 mg/kg was determined in the mouse (ChemCAS 2004).
- *Oral*: An LD_{50} of 105 mg/kg was determined in the rabbit (ChemCAS 2004).
- *Oral*: An LD_{50} of > 15,000 mg/kg-bw was determined for red phosphorus in the rat (ESIS 2000).
- *Oral*: A dosage of 0.66 mg/kg-bw (red phosphorus) did not kill rabbits or guinea pigs, but did induce cirrhosis-like symptoms (Hayes 1991).
- *Inhalation*: An LC_{50} (1 hour exposure time) of 4.3 mg/L (red phosphorus) was determined in the rat (ESIS 2000).

Corrosion/ Irritation (Skin/ Eye) (Cr) Score: (H, M or L): H
Red phosphorus was assigned a score of High for corrosion and irritation based on animal studies that showed the chemical to cause injury to skin and eyes.

- *Dermal*: Prolonged or repeated contact may cause irritation and/or dermatitis (Avogadro 2000).
- *Dermal*: If contaminated with white phosphorus, contact may cause deep, slow healing burns (J.T. Baker 2008).
- *Ocular*: May cause corneal injury (Avogadro 2000).
- *Ocular*: If contaminated with white phosphorus, contact can cause severe irritation and burns (J.T. Baker 2008).

Sensitization (Sn) Score (Skin and Respiratory): (H, M or L): L
Red phosphorus was assigned a score of Low for sensitization because no basis for concern was identified.

- *Dermal*: Red phosphorus is not sensitizing to guinea pigs (ESIS 2000)

Systemic/ Organ (ST) Toxicity Score (includes organ effects and immunotoxicity) (H, M or L): H
Red phosphorus was assigned a score or High for systemic/organ toxicity based on evidence of adverse effects in humans.

- Red phosphorus targets the liver and kidneys (Avogadro 2000).
- Chronic exposure to red phosphorus can lead to necrosis of the jaw or "phossy-jaw" (Avogadro 2000).
- Chronic exposure to red phosphorus can lead to blood disorders and cardiovascular effects (J.T. Baker 2008).
- Persons with pre-existing skin disorders or eye problems, jaw/tooth abnormalities, or impaired liver, kidney or respiratory function may be more susceptible to the effects of red phosphorus (J.T. Baker 2008).
- Mice and rats were exposed to the smoke produced by ignition of a red phosphorus pyrotechnic composition, 1 hr/day, 5 days/week, at two different dose levels (actual doses not provided by the authors), together with controls. The mice received 180 exposures, while the rats received 200 exposures. Guinea pigs also underwent 200 exposures at the lower concentration, but all animals exposed at the higher concentration died during or immediately after the first dose. Growth of the test groups of mice and rats was depressed during the exposure period. Organ specific toxicity appeared not to be present in rats and was generally confined to the respiratory tract of the mice and the guinea pigs. A significantly higher proportion of the test group mouse lung showed aggregates of macrophages containing granules than was present in the control group. Severe congestion was observed in practically all the lung from the decedent high-dose group guinea pigs (Marrs 1989).

Ecotoxicity

Acute Aquatic (AA) Toxicity Score: (H, M or L): L
Red phosphorus was assigned a score of Low for acute aquatic toxicity based on LC_{50} values greater than 100 mg/L.

- An LC_{50} of 2,609 mg/L was identified in fish (96 hour) (U.S. EPA 2009).
- An LC_{50} of 1,051 mg/L was identified in the daphnid (aquatic invertebrate, 48 hour) (U.S. EPA 2009).
- An EC_{50} of 186 mg/L was identified in green algae (aquatic plant, 96 hour) (U.S. EPA 2009).

Chronic Aquatic (CA) Toxicity Score: (H, M or L): M

Red phosphorus was assigned a score of Moderate for chronic aquatic toxicity based on the risk phrase of R52/53,

- Red phosphorus was assigned the following Risk Phrase: R52/53- Harmful to aquatic organisms, may cause long-term adverse effects in the aquatic environment (ChemCAS 2004).
- A ChV of 233 mg/L was identified in fish (30 day) (U.S. EPA 2009).
- A ChV of 85 mg/L was identified in daphnid (U.S. EPA 2009).
- A ChV of 48 mg/L was identified in green algae (U.S. EPA 2009).

Environmental Fate

Persistence (P) Score: (vH, H, M, or L): M
Red phosphorus was assigned a score of Moderate for persistence based on a half-life in soil of 30 days and a half-life in water of 15 days.

- EPI Suite – BIOWIN model results indicate phosphorus readily biodegrades, and has a predicted degradation time of days to weeks. STP removal expected using BIOWIN/EPA Draft Method results indicate 96.32% total removal, with 50.88% due to biodegradation. Fugacity modeling predicts 1.86% partitioning to soil with a half-life of 30 days, and 42.3% partitioning to water with a half-life of 15 days (U.S. EPA 2010a).

Bioaccumulation (B) Score: (vH, H, M, or L): L
Red phosphorus was assigned a score of Low for bioaccumulation based on a BCF less than 500.

- BCFBAF predicts a bioconcentration factor (BCF) of 0.9181 and a log K_{ow} of -0.27 (U.S. EPA 2010a).

Physical Properties

Explosivity (Ex) Hazard Rating: (H, M or L): H
Red phosphorus was assigned a score of High for explosivity based on the risk phrase R16.

- Red phosphorus was assigned the following Risk Phrase: R16- Explosive when mixed with oxidizing substances (Avogadro 2000).
- Lack of oxygen can lead to the formation of white phosphorus which is explosive when in contact with air (Leisewitz 2000).

Flammability (F) Hazard Rating: (H, M or L): H
Red phosphorus was assigned a score of High for flammability based on the risk phrase R11.

- Red phosphorus was assigned the following Risk Phrase: R11- Highly flammable (Avogadro 2000, ChemCAS 2004, J.T. Baker 2008).

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EPI Suite Results: Red Phosphorus:

CAS Number: 7723-14-0
SMILES : P
CHEM : PHOSPHORUS
MOL FOR: H3 P1
MOL WT : 34.00
---------- EPI SUMMARY (v4.00) ----------
Physical Property Inputs:
Log Kow (octanol-water): ------
Boiling Point (deg C) : ------
Melting Point (deg C) : ------
Vapor Pressure (mm Hg) : ------
Water Solubility (mg/L): ------
Henry LC (atm-m3/mole) : ------

Log Octanol-Water Partition Coef (SRC):
*** WARNING: Inorganic Compound (Outside Estimation Domain)
Log Kow (KOWWIN v1.67 estimate) = -0.27

Boiling Pt, Melting Pt, Vapor Pressure Estimations (MPBPVP v1.43):
*** WARNING: Inorganic Compound (Outside Estimate Domain) ***
*** WARNING: Estimations NOT VALID ***
Boiling Pt (deg C): 468.18 (Adapted Stein & Brown method)
Melting Pt (deg C): 162.02 (Mean or Weighted MP)
VP(mm Hg,25 deg C): 2.33E+004 (Mean VP of Antoine & Grain methods)
VP (Pa, 25 deg C) : 3.11E+006 (Mean VP of Antoine & Grain methods)
MP (exp database): -133 deg C
BP (exp database): -87.7 deg C
VP (exp database): 2.93E+04 mm Hg (3.91E+006 Pa) at 25 deg C

Water Solubility Estimate from Log Kow (WSKOW v1.41):
*** WARNING: Inorganic Compound (Outside Estimation Domain)**
Water Solubility at 25 deg C (mg/L): 2.048e+005
log Kow used: -0.27 (estimated)
no-melting pt equation used
Water Sol (Exper. database match) = 3.3 mg/L (15 deg C)
Exper. Ref: KIRK-OTHMER; on-line (2005)

Water Sol Estimate from Fragments:
*** WARNING: Inorganic Compound (Outside Estimation Domain)***
*** WARNING: Wat Sol Estimation NOT Valid ***
Wat Sol (v1.01 est) = 60349 mg/L

ECOSAR Class Program (ECOSAR v1.00):
Class(es) found: Neutral Organics

Henrys Law Constant (25 deg C) [HENRYWIN v3.20]:
*** WARNING: Inorganic Compound (Outside Estimation Domain) **
*** WARNING: Estimation NOT VALID **
Bond Method : 2.44E-002 atm-m3/mole (2.48E+003 Pa-m3/mole)
Group Method: Incomplete
For Henry LC Comparison Purposes:
User-Entered Henry LC: not entered
Henrys LC [via VP/WSol estimate using User-Entered or Estimated values]:
HLC: 1.660E-004 atm-m3/mole (1.682E+001 Pa-m3/mole)

VP: 2.33E+004 mm Hg (source: MPBPVP)
WS: 2.05E+005 mg/L (source: WSKOWWIN)

Log Octanol-Air Partition Coefficient (25 deg C) [KOAWIN v1.10]:
*** WARNING: Inorganic Compound (Outside Estimation Domain)**
*** WARNING: Estimation NOT VALID ***
Log Kow used: -0.27 (KowWin est)
Log Kaw used: -0.001 (HenryWin est)
Log Koa (KOAWIN v1.10 estimate): -0.269
Log Koa (experimental database): None

Probability of Rapid Biodegradation (BIOWIN v4.10):
*** WARNING: Inorganic Compound (Outside Estimation Domain)**
*** WARNING: Estimation NOT VALID ***
Biowin1 (Linear Model) : 0.7314
Biowin2 (Non-Linear Model) : 0.9259
Expert Survey Biodegradation Results:
Biowin3 (Ultimate Survey Model): 3.1240 (weeks)
Biowin4 (Primary Survey Model) : 3.7987 (days)
MITI Biodegradation Probability:
Biowin5 (MITI Linear Model) : 0.6110
Biowin6 (MITI Non-Linear Model): 0.8241
Anaerobic Biodegradation Probability:
Biowin7 (Anaerobic Linear Model): 0.8361
Ready Biodegradability Prediction: YES

Hydrocarbon Biodegradation (BioHCwin v1.01):
Structure incompatible with current estimation method!

Sorption to aerosols (25 Dec C)[AEROWIN v1.00]:
Vapor pressure (liquid/subcooled): 3.91E+006 Pa (2.93E+004 mm Hg)
Log Koa (Koawin est): -0.269
Kp (particle/gas partition coef. (m3/ug)):
Mackay model : 7.68E-013
Octanol/air (Koa) model: 1.32E-013
Fraction sorbed to airborne particulates (phi):
Junge-Pankow model : 2.77E-011
Mackay model : 6.14E-011
Octanol/air (Koa) model: 1.06E-011

Atmospheric Oxidation (25 deg C) [AopWin v1.92]:
*** WARNING: Inorganic Compound (Outside Estimation Domain)***
Hydroxyl Radicals Reaction:
OVERALL OH Rate Constant = 0.0000 E-12 cm3/molecule-sec
Half-Life = -------
Ozone Reaction:
No Ozone Reaction Estimation
Fraction sorbed to airborne particulates (phi):
4.46E-011 (Junge-Pankow, Mackay avg)
1.06E-011 (Koa method)
Note: the sorbed fraction may be resistant to atmospheric oxidation

Soil Adsorption Coefficient (KOCWIN v2.00):
*** WARNING: Inorganic Coumpound (Outside Estimation Domain) **
*** WARNING: Estimation NOT VALID **
Koc : 13.22 L/kg (MCI method)
Log Koc: 1.121 (MCI method)

Koc : 0.5825 L/kg (Kow method)
Log Koc: -0.235 (Kow method)

Aqueous Base/Acid-Catalyzed Hydrolysis (25 deg C) [HYDROWIN v2.00]:
Rate constants can NOT be estimated for this structure!

Bioaccumulation Estimates (BCFBAF v3.00):
Log BCF from regression-based method = 0.500 (BCF = 3.162 L/kg wet-wt)
Log Biotransformation Half-life (HL) = -1.7075 days (HL = 0.01961 days)
Log BCF Arnot-Gobas method (upper trophic) = -0.037 (BCF = 0.9181)
Log BAF Arnot-Gobas method (upper trophic) = -0.037 (BAF = 0.9181)
log Kow used: -0.27 (estimated)

Volatilization from Water:
Henry LC: 0.0244 atm-m3/mole (estimated by Bond SAR Method)
Half-Life from Model River: 0.609 hours (36.54 min)
Half-Life from Model Lake : 55.54 hours (2.314 days)

Removal In Wastewater Treatment:
Total removal: 90.47 percent
Total biodegradation: 0.02 percent
Total sludge adsorption: 0.39 percent
Total to Air: 90.06 percent
(using 10000 hr Bio P,A,S)

Removal In Wastewater Treatment (recommended maximum 95%):
Total removal: 96.32 percent
Total biodegradation: 50.88 percent
Total sludge adsorption: 0.27 percent
Total to Air: 45.18 percent
(using Biowin/EPA draft method)

Level III Fugacity Model:

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	55.7	1e+005	1000
Water	42.3	360	1000
Soil	1.86	720	1000
Sediment	0.101	3.24e+003	0

Persistence Time: 146 hr

ECOSAR Results: Red Phosphorus:

SMILES : P
CHEM : PHOSPHORUS
CAS Num: 007723-14-0
ChemID1:
ChemID2:
ChemID3:
MOL FOR: H3 P1
MOL WT : 34.00
Log Kow: -0.27 (KowWin estimate)
Melt Pt:
Wat Sol: 3.3 mg/L (experimental database)

ECOSAR v1.00 Class(es) Found

Neutral Organics

ECOSAR Class	Organism	Predicted Duration	End Pt	mg/L (ppm)
Neutral Organics	: Fish	96-hr	LC50	2609.779 *
Neutral Organics	: Fish	14-day	LC50	2543.939 *
Neutral Organics	: Daphnid	48-hr	LC50	1051.975 *
Neutral Organics	: Green Algae	96-hr	EC50	186.249 *
Neutral Organics	: Fish	30-day	ChV	233.517 *
Neutral Organics	: Daphnid		ChV	85.106 *
Neutral Organics	: Green Algae		ChV	48.739 *
Neutral Organics	: Fish (SW)	96-hr	LC50	4311.682 *
Neutral Organics	: Mysid Shrimp	96-hr	LC50	13151.021 *
Neutral Organics	: Fish (SW)		ChV	103.053 *
Neutral Organics	: Mysid Shrimp (SW)		ChV	2228.113 *
Neutral Organics	: Earthworm	14-day	LC50	101.661 *

Note: * = asterisk designates: Chemical may not be soluble enough to measure this predicted effect.

Neutral Organics:

For Fish LC50 (96-h), Daphnid LC50, Mysid: If the log Kow is greater than 5.0, or if the compound is solid and the LC50 exceeds the water solubility by 10X, no effects at saturation are predicted.

For Fish LC50 (14-day) and Earthworm LC50: If the log Kow is greater than 6.0, or if the compound is solid and the LC50 exceeds the water solubility by 10X, no effects at saturation are predicted.

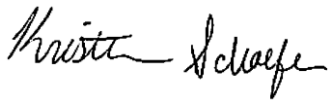
For Green Algae Acute Toxicity Values: If the log Kow of the chemical is greater than 6.4, or if the compound is solid and the EC50 exceeds the water solubility by 10X, no effects at saturation are predicted for these endpoints.

For All Chronic Toxicity Values: If the log Kow of the chemical is greater than 8.0, or if the compound is solid and the ChV exceeds the water solubility by 10X, no effects at saturation are predicted for these endpoints.

ECOSAR v1.00 SAR Limitations:

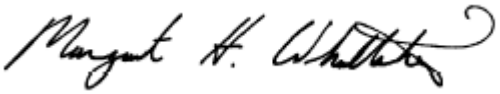
Maximum LogKow: 5.0 (Fish 96-hr LC50; Daphnid LC50, Mysid LC50)
Maximum LogKow: 6.0 (Fish 14-day LC50; Earthworm LC50)
Maximum LogKow: 6.4 (Green Algae EC50)
Maximum LogKow: 8.0 (ChV)
Maximum Mol Wt: 1000

Red Phosphorus Green Screen Evaluation Prepared By:



Kristen Schaefer, M.F.S.
Associate Toxicologist
ToxServices LLC

Red Phosphorus Green Screen Evaluation QC'd By:

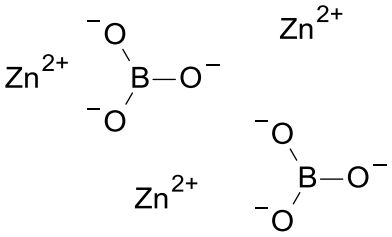


Margaret H. Whittaker, Ph.D., M.P.H., E.R.T., D.A.B.T.
Managing Director and Chief Toxicologist
ToxServices LLC

APPENDIX IX J: GREEN SCREEN FOR ZINC BORATE (CAS #1332-07-6)[28]

Also Called: Alcanex FR 100, Alcanex FRC 600, Bonrex FC, Borax 2335, Boric acid, zinc salt, Climax ZB 467, EINECS 215-566-6, EPA Pesticide Chemical Code 128859, FRC 600, Flamtard Z 10, HSDB 1046, JS 9502, SZB 2335, XPI 187, ZB 112, ZB 237, ZB 467 Lite, ZN 100, ZSB 2335, ZT, ZT (fire retardant), Zinc borate

Chemical Structure of Zinc Borate:



***Note:** Data gaps for this chemical were addressed by evaluating the toxicity data on zinc oxide (CAS #1314-13-2) and boric acid (CAS #10043-35-3; 11113-50-1). ToxServices selected these chemicals as they are degradation products of the parent compound and structurally similar to the parent compound.

For Inorganic Chemicals:
Define Form & Physiochemical Properties
16. Particle size (e.g. silica of respirable size) – 8-20 □article size (e.g. silic
17. Structure (e.g. amorphous vs. crystalline) – n/a
18. Mobility (e.g. Water solubility, volatility) – 0.1% at pH 5 and 7, and 0.03% at pH 9 (U.S. EPA 1991)

Identify Applications/Functional Uses: Flame retardant.

Green Screen Rating[29]: Zinc borate was assigned a Benchmark Score of 2 based on a Moderate hazard rating for reproductive and developmental (R/D) toxicity (1d).

Green Screen (Version 1.0) Levels of Concern for Zinc Borate														
Human – Tier 1					Human – Tier 2				Eco		Fate		Physical	
C	M	R/D	ED	N	AT	Cr	Sn	ST	AA	CA	P	B	Ex	F
L	L	*M*	*M*	nd	L	M	L	M	H	nd	nd	L	L	L

*Endpoints in italics were assigned using estimated values and professional judgment (Structure Activity Relationships).

[28] CPA recommends independent third-party validation of all Green Screen assessments. No independent third-party validation has been done for this assessment . Companies may not make marketing claims based on a Green Screen assessment that has not undergone an independent validation.
[29] For inorganic chemicals with low human and ecotoxicity across all hazard endpoints and low bioaccumulation, persistence alone will not be deemed problematic. Inorganic chemicals that are only persistent will be evaluated under the criteria for Benchmark 4.

Transformation Products and Ratings:
Identify relevant fate and transformation products (i.e., dissociation products, transformation products, valence states) and/or moieties of concern[30]

Life Cycle Stage	Transformation Pathway	Transformation Products	CAS #	Green Screen Rating
End of Life	Dissociation	Zinc, cation	23713-49-7	Not present on the Red List of Chemicals (CPA 2009)
End of Life	Dissociation	Borate, anion	39201-27-9	Not present on the Red List of Chemicals (CPA 2009)
End of Life	Degradation	Zinc oxide	1314-13-2	Not present on the Red List of Chemicals (CPA 2009)
End of Life	Degradation	Boric acid	10043-35-3; 11113-50-1	Endocrine Disruptor (CPA 2009)

*The above transformation products were screened against the CPA's table of Red List chemicals (CPA 2009).

Introduction

Zinc borate is used as a flame retardant in conjunction with other chemicals, including antimony trioxide, magnesium hydroxide, alumina trihydrate, and some brominated flame retardants. Zinc borate is used as a flame retardant on commercial furniture, draperies, wall coverings, and carpets (R.C.Kidder, Flame Retardant Chemical Association, unpublished material, April 21, 1998). In addition, zinc borate is used as a fungicide (NAS 2000).

A literature search identified limited publications relating to the toxicity of zinc borate. However, variety of toxicological studies have been performed on various inorganic borates. Longer-term toxicological studies have been reported, and are mainly on boric acid or borax. There is similarity in the toxicological effects of boric acid and borax across different animal species (Hubbard 1998).

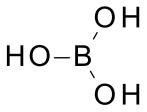
Additionally, zinc borate readily breaks down in the stomach to zinc oxide (ZnO) and boric acid (H_3BO_3) (NAS 2000). Therefore, in the absence of data for zinc borate, the data for zinc oxide and boric acid will be substituted. Zinc oxide is used as a pigment in paint, cosmetics, and dental and quick drying cements. Therapeutically, zinc oxide is

[30] A moiety is a discrete chemical entity that is a constituent part or component of a substance. A moiety of concern is often the parent substance itself for organic compounds. For inorganic compounds, the moiety of concern is typically a dissociated component of the substance or a transformation product.

used as an astringent and as a topical protectant. Boric acid is used in enamels, porcelain, soaps, cosmetics, and as an insecticide. Therapeutically, boric acid is used as an astringent and an antiseptic (NAS 2000).

The critical health effect endpoints in several species are male reproductive toxicity and developmental toxicity. Humans would need to consume daily doses of 3.3 g of boric acid (or 5.0 g borax) to ingest the same dose level as the lowest animal NOAEL. No effects on fertility were seen in a population of workers exposed to borates or to a population exposed to high environmental borate levels (Hubbard 1998).

Chemical Structure of Surrogates



Boric Acid (CAS #10043-35-3; 11113-50-1)

Zinc Oxide (CAS #1314-13-2)

Human Health – Tier 1

Carcinogenicity (C) Score (H, M or L): L

Because carcinogenicity data were unavailable for zinc borate, the structurally similar zinc oxide and boric acid were used as surrogates. Zinc borate was assigned a score of Low for carcinogenicity based on negative results from surrogate studies.

Zinc borate

- Not listed as a known carcinogen by IARC, NTP, U.S. EPA, or CA Prop 65.

Zinc oxide

- Not classifiable as to human carcinogenicity due to inadequate evidence in humans and animals (U.S. EPA 2005).

Boric acid

- In long term feeding studies on boric acid and disodium tetraborate decahydrate in both rats and dogs, no carcinogenic effects were observed (Weir and Fisher 1972). In rats, diets contained disodium tetraborate decahydrate or boric acid at 0, 117, 350, and 1,170 ppm boron equivalents for 2 years; these doses were approximately 0, 5.9, 17.5 or 58.5 mg B/kg bw/day. Effects observed in these rat studies included lowered food consumption, retarded body weight gain, course hair coats, haunched position, swollen pads, inflamed bleeding eyes and changes in haematological parameters at the highest doses (58.5 mg B/kg bw/day). Dogs were fed diets containing boric acid (0.033%, 0.067%, 0.2% in diet) or disodium tetraborate decahydrate at (0.051%, 0.103%, 0.309%). No evidence of toxicity was observed. Therefore, additional groups of dogs (4 male and 4 female) were fed diets containing 0.67% boric acid or 1.03% disodium tetraborate decahydrate. The estimated equivalent boron intakes from the boric acid diet were 1.7, 3.8, 10.9 and 40.8 mg B/kg bw/day and from the disodium tetraborate decahydrate diet were 1.9, 3.6, 9.6 and 38.1.mg B/kg bw/day. In dogs, diarrhea was observed in some and soft stools in all dogs at the highest dose tested. Testicular effects

were observed in both rats and dogs. Testicular atrophy with some interstitial cell hyperplasia was the critical effect seen in a US National Toxicology Program (NTP) bioassay in mice (dose levels in food 0, 2,500, 5,000 ppm boric acid). No carcinogenic effects were observed at these doses estimated to be equivalent to 78 mg B/kg bw/day and 201 mg B/kg bw/day (NTP 1987). Effects on survival rate and reduced body weight gain were seen at the high doses. The studies carried out are not to modern standards, nor to GLP. However, they are well performed and reported, and are more than adequate to evaluate the carcinogenicity of boric acid and sodium tetraborates. It can be concluded that boric acid and sodium tetraborates are not carcinogenic and there is no concern for a carcinogenic effects in humans (HERA 2005).

Mutagenicity (M) and Genotoxicity Score (H, M or L): L

Because mutagenicity and genotoxicity data for zinc borate are limited, additional data for zinc oxide and boric acid are included. Zinc borate was assigned a score of Low for mutagenicity and genotoxicity based on negative mutagenicity results.

Zinc borate

- Zinc borate did not induce either genotoxic effects or chromosomal aberrations in mutagenicity studies (U.S. EPA 1991).
- In the Salmonella/microsomal assay (Ames assay) for bacterial mutagenic activity, zinc borate did not elicit any mutagenic response in *Salmonella* tester strains when tested either with or without a metabolic activation system (the EPA did not identify specific strains or concentrations) (U.S. EPA 1991).

Zinc oxide

- Several studies were identified that investigated the genotoxicity of zinc oxide. Data on other zinc compounds are relevant for a hazard evaluation based on the assumption that after intake the biological activities of zinc compounds are determined by the zinc cation. Available data indicate that the genotoxicity results vary widely. Conflicting results have been found, even in the same test systems. Overall, the results of the *in vitro* tests indicate that zinc has genotoxic potential. This is based on positive results in mammalian test systems for gene mutations and chromosomal aberrations as well as on the positive *in vitro* UDS test. *In vivo* increases in chromosomal aberrations were found in calcium-deficient mice exposed via the diet as well as in mice with normal calcium status when dosed intraperitoneally. Additionally, negative results were obtained in mice at higher intraperitoneal dose levels. Rats tested negative for chromosomal aberrations after oral dosing, either via gavage or via the diet. The positive result for chromosomal aberrations *in vitro* is considered overruled by negative *in vivo* tests for this endpoint. The positive sperm head abnormality test is considered sufficiently counter-balanced by two negative SLRL tests as well as two negative dominant lethal tests. Moreover, this sperm test is not adequately reported and without details on scoring criteria, interpretation of the observations is rather subjective. In addition, sperm head abnormalities are indicative rather than proof for genotoxicity. Based on the available data there is insufficient ground to classify zinc as genotoxic. It should be noted that the potential to induce gene mutations was not adequately tested *in vivo*. However, there is no clear evidence from the available data that zinc is genotoxic *in vivo* and, without a clear

indication for carcinogenicity, guidance for further testing with respect to target tissue is not available (ESIS 2008).

Boric acid

- A number of *in vitro* mutagenicity studies, including bacterial mutation assays in Salmonella typhimurium and Escherichia coli, gene mutation in mammalian cells (L5178Y mouse lymphoma, V79 Chinese hamster cells, C3H/10T1/2 cells), bacterial DNA-damage assay, unscheduled DNA synthesis (hepatocytes), chromosomal aberration and sister chromatid exchange in mammalian cell (Chinese hamster ovary, CHO cells) have been carried out on boric acid, disodium tetraborate decahydrate or disodium octaborate tetrahydrate. No evidence of mutagenic activity was observed (NTP 1987; Haworth et al. 1983; Landolph 1985; Bakke 1991; Stewart 1991).
- No mutagenic activity was seen *in vivo* in a mouse bone marrow micronucleus study on boric acid (O'Loughlin 1991).

Reproductive (R) and Developmental (D) Toxicity Score (H, M or L): *M*

Because reproductive and developmental toxicity data were unavailable for zinc borate, the structurally similar zinc oxide and boric acid were used as surrogates. Zinc borate was assigned a score of Moderate for reproductive and developmental toxicity based on developmental effects reported in rats, mice and rabbits exposed to boric acid (H_3BO_3). The most sensitive species appears to be rats, in which the effects observed at non-maternally toxic doses include a reduction in fetal body weight and minor skeletal variations.

Zinc borate

- No relevant reproductive and developmental toxicity data were identified for zinc borate.

Zinc oxide

- Groups of Sprague-Dawley rats (10/group) were fed diets containing 2,000 or 5,000 mg ZnO/kg feed (calculated to be 150 or 375 mg ZnO/kg bw [≈120 or 300 mg Zn^{2+}/kg bw/day]) from day 0 of gestation to day 14 of lactation, then mothers and remaining pups were killed. The control animals received a basal diet containing 9 mg Zn^{2+}/kg feed. Maternal weight, daily food intake, duration of gestation, and the number of viable young/litter were not affected. No external malformations were seen. Two females at 5,000 mg/kg feed had all stillborn litters containing edematous pups. At 2,000 mg/kg feed, 4 stillborn pups (not edematous) were observed. Dry liver weights of pups (newborn and 14 days old) were decreased at 5,000 mg/kg feed. A dose-related increase in zinc content and a dose-related decrease in iron content were observed. The livers of newborns of zinc-treated dams, however, contained significantly more iron than the controls. This was not observed in the 14-day old pups. The copper levels in the liver were significantly lower only in the newborns of the 5,000 mg/kg level. After 14 days the copper concentrations were significantly lower in all treated pups (Ketcheson et al. 1969).
- Bleavins et al. (1983) exposed groups of mink (11 females and 3 males/group) to a basal diet (containing 20.2 mg Zn^{2+}/kg diet and 3.1 mg Zn^{2+}/kg diet) or to the diet supplemented with 1,000 mg ZnO/kg diet. No maternal effects were seen. All females on the basal diet produced offspring, 8/11 females of the Zn-

supplemented diet group had young. None of the animals (males, females and kits) were sacrificed, so they were only macroscopically examined. The kits were kept on the basal and supplemented diets. The body weight of male kits on the supplemented diet was significantly lower at 12 weeks of age. 8-Week old kits on the supplemented diet showed a significant decrease of the Ht-value, the other blood parameters were comparable to the kits on basal diet. The decreased T-cell mitotic response observed in the Zn-supplemented kits was reversible when the kits were placed on basal diet. Kits (3-4 weeks old) of females fed the Zn-supplemented diet showed effects consistent with copper deficiency, such as grey fur around eyes, ears, jaws and genitals together with hair loss and dermatosis in these areas.

- Hence, with respect to effects on reproduction, zinc deficiency is known to result in impairment of fertility and of fetal development. In humans additional zinc up to 0.3 mg Zn^{2+}/kg bw/day during pregnancy did not result in adverse effects. Available data in animals on zinc excess indicate that adverse effects on fertility and fetal development may occur at dose levels of 200 mg Zn^{2+}/kg bw/day, in conjunction with other effects such as perturbation of parental and fetal copper homeostasis. In humans, a small disturbance (if any) of normal physiology, presumably indicative for copper deficiency, has been demonstrated at zinc excess of 50 and 150 mg Zn^{2+}/day (0.83 and 2.5 mg Zn^{2+}/kg bw/day, respectively), while 150 mg Zn^{2+}/day (2.5 mg Zn^{2+}/kg bw/day) resulted in clinical signs. As the margin between the dose at which in humans clinical signs are manifested and the dose at which in animals reproductive effects have been reported is so high (viz. 80), it is considered unlikely that in humans reproductive effects will occur at exposure levels at which clinical signs are not manifest. Therefore, neither fertility nor developmental toxicity is considered end-points of concern for humans. Based on the available information there is no reason to classify metallic zinc nor any of the zinc compounds considered for reproductive toxicity.

Boric acid

- Effects on the testis have been observed in both sub-chronic and chronic studies in three species: rats, mice and limited studies in dogs. In rats, a single dose of 175 mg B/kg bw was found to cause reversible disruption of tubular spermiation (Linder et al. 1990), although no such effects were observed after a single dose of 350 mg B/kg (2,000 mg boric acid/kg) (Bouissou and Castagnol 1965). The effects tend to be similar in all three species, although most data comes from rat studies. The reproductive effects in rats at lower doses and shorter time periods start with reversible inhibition of spermiation. Early effects were seen after 14 days treatment, at doses around 39 mg B/kg, (217 mg boric acid/kg bw/day) but at a lower dose of 26 mg B/kg (149 mg boric acid/kg bw/day) the effects take about 28 days to manifest (Ku et al. 1993). In a rat three generation study of boric acid and disodium tetraborate decahydrate, doses equivalent to 58.5 mg B/kg bw/day led to testicular atrophy, degeneration of seminiferous tubules, reduced sperm count and a reduction in fertility, with a NOAEL of 17.5 mg B/kg bw/day (Weir and Fisher 1972). Similar results were seen in a two-year study of boric acid and disodium tetraborate decahydrate at 58.5 mg B/kg bw/day where the NOAEL was also 17.5 mg B/kg bw/day (Weir and Fisher 1972). In male rats fed disodium

tetraborate decahydrate for either 30 or 60 days at 100 or 200 mg B/kg bw/day testis weight was reduced, testicular germ cells were depleted, selected testicular enzymes were affected and fertility was reduced. The NOAEL was 50 mg B/kg bw/day (Lee et al. 1978). As might be expected, while recovery from inhibition of spermiation occurred at the lower doses, there was no recovery from testicular atrophy when the germ cells were lost.

- Data in dogs derives from two very limited and unreliable two-year dietary studies. Unfortunately, the published study does not accurately reflect the original study reports (Weir and Fisher 1972). In the published paper, the authors estimated the dietary intakes from standard intake figures. However, actual dietary intake was reported in the original study reports allowing a more accurate measure of the dietary intake to be made which are used in this review. Groups of only four male dogs were fed either boric acid or disodium tetraborate decahydrate at doses up to 10.2 mg B/kg bw/day (62.4 mg boric acid/kg bw/day and 84.7 mg disodium tetraborate decahydrate/kg bw/day) in one study and 39.5 mg B/kg bw/day (233.1 mg boric acid/kg bw/day and 373.2 mg disodium tetraborate decahydrate/kg bw/day) in a second study. The animals were sacrificed at various time periods such that observations were reported on only 1 or 2 animals. At 39.5 mg B/kg bw/day, testicular atrophy was observed, however the effects in the only one disodium tetraborate decahydrate treated dog investigated at 38 weeks were less severe than those seen in the control dog. Also, testicular atrophy was present in three out of four control dogs, so that the significance of the effect in the treated animals is difficult to assess. One boric acid treated and one disodium tetraborate decahydrate treated dog were allowed to recover for three weeks. Some recovery was observed in each dog. Minor histopathological changes such as decreased spermatogenesis remained which was less obvious in the disodium tetraborate decahydrate treated dog. The NOAEL was deemed to be the equivalent of 10.2 mg B/kg bw/day by the authors (Weir 1966 a,b; 1967 a,b; Weir and Fisher 1972). For the reasons given above (effects in control animals, insufficient group sizes, inaccurate dose reporting), this data is not reliable for risk assessment, but it does confirm the effects seen in other species. Due to the acute toxic effects of borates in dogs, had the LOAEL doses been administered as a single dose (i.e. by gavage) then vomiting would have occurred and the study would not have been possible.
- A dose-related effect on the testis was observed in rats and mice with confirmation from limited and unreliable studies in dogs. Effects start with reversible inhibition of spermiation after 14 days treatment, at doses around 39 mg B/kg, (217 mg boric acid/kg bw/day) although at a lower dose of 26 mg B/kg (149 mg boric acid/kg bw/day) the effects take about 28 days to manifest. Higher doses (58.5 mg B/kg bw/day and above) led to testicular atrophy, degeneration of seminiferous tubules, reduced sperm count and a reduction in fertility. No recovery from testicular atrophy was observed when the germ cells were lost. The NOEL for this endpoint is 17.5 mg B/kg corresponding to 100 mg boric acid/kg/day; 155 mg disodium tetraborate decahydrate/kg and 118 mg disodium tetraborate pentahydrate/kg (HERA 2005).
- The majority of developmental toxicity studies have been carried out in rats exposed to boric acid (H_3BO_3). In two separate dietary studies performed in the

same laboratory, groups of rats were given dose levels of approximately 3.3, 6.3, 9.6, 13.7, 25, 28 and 59 mg B/kg bw/day on gestation days 0-20 and 94 mg B/kg bw/day on gestation days 6-15 in feed. The NOAELs for maternal toxicity and developmental effects were 13.7 mg/kg bw/day and 9.6 mg B/kg bw/day (equivalent to 54.9 mg H_3BO_3/kg-bw)[31], respectively. A reduction in food intake and an increase in relative liver and kidney weight and a reduction in maternal body weight gain at higher doses indicated maternal toxicity. At non-maternally toxic doses, there was a reduction on fetal weight and some skeletal variations and malformations (increase in wavy ribs and short rib XIII and a decreased incidence of rudimentary extra rib on lumbar 1), which had reversed by postnatal day 21 at 13.7 mg B/kg bw/day also, with the exception of short rib XIII, had reversed at 28.6 mg B/kg bw/day in a study designed to look at postnatal recovery (Price et al. 1990, 1996). At higher maternally toxic doses, other indications of developmental effects were observed, including resorptions and visceral malformations (enlarged lateral ventricles; cardiovascular effects; anophthalmia and microphthalmia and short and curly tails). However, these are likely to have been secondary to the maternal toxicity (Price et al. 1990, 1996; Heindel et al. 1992).

- Similar findings were observed in mice receiving estimated doses of 0, 43, 79, and 175 mg B/kg bw/day on gestation days 0-20 in feed. Maternal toxicity was indicated by a dose related incidence of renal tubule dilation/regeneration and at the highest dose increases food and water consumption in late gestation and in the relative kidney weight. A NOAEL was not determined for maternal toxicity. The key developmental effects observed were similar to those seen in rats i.e. a reduction in foetal body weight at the mid dose (79 mg B/kg) and an increase in skeletal variations and malformations (missing lumbar vertebrae, fused vertebral arches and short rib XIII) and resorptions at the highest, more maternally toxic dose. The NOAEL for developmental effects in mice was 43 mg B/kg bw/day (Heindel et al. 1992); however, this dose was also a maternally toxic dose.
- In rabbits receiving estimated doses of 0, 11, 22 and 44 mg B/kg bw/day by gavage on gestation days 6-19 maternal toxicity was indicated by effects such as an increase in relative kidney weight, increase food intake, vaginal bleeding and an increase in corrected weight gain. Developmental effects were seen only at the top dose, where the majority of the embryos were resorbed and malformations were primarily visceral (major heart and/or great vessel defects); however, these effects are likely to be secondary to the maternal toxicity. The only skeletal effect observed was a decreased incidence of rudimentary extra rib on lumbar 1 which was not considered biologically significant. The NOAEL for both maternal and developmental toxicity in the rabbit was 21.8 mg B/kg bw/day (Price et al. 1991).
- Developmental effects have been observed in three species, rats, mice and rabbits. The most sensitive species appears to be rats, in which the effects observed at non-maternally toxic doses include a reduction in fetal body weight and minor skeletal variations which, with the exception of short rib XIII, had reversed by 21

[31] $\frac{9.6\ mg\ B}{kg\ bw} * \frac{g\ B}{1{,}000\ mg\ B} * \frac{mol\ B}{10.811\ g\ B} * \frac{mol\ H_3BO_3}{mol\ B} * \frac{61.83302\ g\ H_3BO_3}{mol\ H_3BO_3} * \frac{1{,}000\ mg\ H_3BO_3}{g\ H_3BO_3} = 54.9 \frac{mg\ H_3BO_3}{kg\ bw}$

days post natal. The NOAEL for developmental effects is 9.6 mg B/kg (HERA 2005).

Endocrine Disruption (ED) Score (H, M or L): *M*

Because endocrine disruption data were unavailable for zinc borate, the structurally similar zinc oxide and boric acid were used as surrogates. Zinc borate was assigned a score of Moderate for endocrine disruption based on suggestive animal studies for boric acid and the presence of boric acid on the European Union Priority List of Suspected Endocrine Disruptors.

Zinc borate

- Not listed as a potential endocrine disruptor on the EU Priority List of Suspected Endocrine Disruptors.
- Not listed as a potential endocrine disruptor on the OSPAR List of Chemicals of Possible Concern.
- Not listed as a potential endocrine disruptor on the Red List of Chemicals (CPA 2009).

Zinc oxide

- No relevant data were identified.

Boric acid

- The majority of toxicological studies have been reported on boric acid (H_3BO_3) or disodium tetraborate, known as borax ($Na_2B_4O_710H_2O$). The inorganic borates display low acute toxicity orally, dermally or by inhalation. They are either not irritant or mild skin and eye irritants. They are not skin sensitizers, nor are they mutagenic or carcinogenic. In sub acute and chronic studies of boric acid in rats, mice, and dogs, the target organ is the testis. Effects on reproductive organs in females were seen, but at higher doses than in males. Effects on fertility were also seen in rats in a three-generation study and in mice in a continuous breeding study. The testicular effects observed include reduction in sperm count, inhibition of spermiation, and testicular atrophy. Reversal of inhibition of spermiation and reduced sperm count in rats was seen after removal of treatment at 38 mg B/kg bw/day (equivalent to 217 mg/kg bw/day boric acid). Minimal inhibition of spermiation was observed at 26 mg B/kg bw/day. A dose of 17 mg B/kg bw/day in male rats (equivalent to 97 mg/kg bw/day boric acid) was the NOAEL. Developmental toxicity has also been demonstrated in mice, rats and rabbits, with rats the most sensitive species. Administration of a wide range of doses of boric acid to pregnant rats for the whole of gestation has shown that at doses of 330 mg/kg bw/day (equivalent to 58 mg B/kg bw/day) and above, there is a high resorption rate and retardation of fetal development. At a lower dose of 28 mg B/kg bw/day, the only effects observed were reduced fetal weight and short 13th rib and wavy rib. These effects disappear if the pups are allowed to be delivered and reared to weaning. The NOAEL was 9.6 mg B/kg bw/day (equivalent to 54 mg/kg bw/day boric acid) (Hubbard 1995).
- To assess whether or not male reproductive toxicity can be evaluated in a 2 week administration study, boric acid was administered daily by oral gavage to male Jcl:Wistar rats at dosage levels of 0, 300, and 500 mg/kg for 2 and 4 weeks, and the results obtained with the 2 different treatment schedules were compared. After a 2 week administration, decreased testis weights were observed in the 500

mg/kg group. Histopathologically, exfoliation of round spermatids, retention of step 19 spermatids, and increased numbers of residual body-like structures in the seminiferous tubules and cell debris in the cranial epididymal ducts were observed in the 300 and 500 mg/kg groups. Distorted cytoplasmic lobes of step 19 spermatids, debris in the seminiferous tubules, and focal atrophy of the seminiferous tubules with multinucleated giant cells formation and necrosis of spermatocytes were also observed in the 500 mg/kg group. After a 4 week administration, testis and epididymis weights were decreased in the 300 and 500 mg/kg groups. Histopathological changes in the 300 mg/kg group were similar to those found in the 300 and 500 mg/kg groups after a 2 week administration. Diffuse atrophy of the seminiferous tubules was additionally observed in the 500 mg/kg group. These results suggest that 2 week is a sufficient treatment period for the detection of the testicular toxicity caused by boric acid (Fukuda et al. 2000).

Neurotoxicity (N) Score (H, M or L): nd

Because neurotoxicity data were unavailable for zinc borate, the structurally similar zinc oxide and boric acid were used as surrogates. No relevant neurotoxicity data were identified for zinc borate, zinc oxide, or boric acid.

Zinc borate

- Not classified as a developmental neurotoxicant (Grandjean and Landrigan 2006).
- Not listed as a potential neurotoxicant on the Red List of Chemicals (CPA 2009).

Zinc oxide

- Special studies were conducted to examine the morphological and histoenzymatic changes of the brain. Twelve Wistar rats were given daily doses of 100 mg ZnO (ca. 600 mg ZnO/kg bw ≈w480 mg Zn2+/kg bw) intragastrically for 10 consecutive days. A control group was included. After 10 days the rats were sacrificed and the brains were examined for morphological and histoenzymatic changes. Morphological changes included degenerative changes of neurocytes, accompanied with moderate proliferation of the oligodendroglia, and glial proliferation in the white matter. Furthermore, endothelial edema was observed in the small arterial and capillary walls. Histoenzymatic changes included decreased activities of ACP (acid phosphatase), ATPase (adenosinetriphosphatase), AChE (acetylcholine esterase), and BChE (Butyrylthiocholineesterase). The activities of TTPase (thiamine pyrophophatase) and NSE (non-specific esterase) were increased. No details on quantitative aspects of enzymatic changes were given. No change was seen in the alkaline phosphatase. The authors indicated that observed morphological and histoenzymatic changes were unspecific, undistinctive and most likely reversible (Kozik et al. 1980). Examination of the neurosecretory function of the hypothalamus and the hypophysis in these animals showed an increased neurosecretion in cells of the supraoptic and paraventricularnucleus of the hypothalamus along with a declined neurosecretion in the hypophysis and an enhanced release of antidiuretic hormone in the neurohypophysis (Kozik et al. 1981). It is not clear whether these observations represent an adverse effect of zinc on the brain or whether they are secondary to changes somewhere else in the body.

Boric acid

- No relevant neurotoxicity data were identified for boric acid.

Human Health – Tier 2

Acute Mammalian (AT) Toxicity Score (H, M or L): L

Zinc borate was assigned a score of Low for acute mammalian toxicity based on oral and dermal LD50 values greater than 2,000 mg/kg-bw. This score is based on data from 3 routes of exposure in two different species of animals.

- *Oral*: An LD_{50} of >10,000 mg/kg was determined in rats (U.S. EPA 1991).
- *Oral*: An LD_{50} of >5,000 mg/kg was determined in rats (Cerven 1992).
- *Oral*: An LD_{50} of >10,000 mg/kg was determined in rats (Daniels et al. 1969).
- *Dermal*: An LD_{50} of >10,000 mg/kg in both male and female albino rabbits (U.S. EPA 1991).
- *Inhalation*: An LD_{50} of > 5 mg/L was determined (species unspecified) (EFRA 2006).

Corrosion/Irritation (Skin/ Eye) (Cr) Score (H, M or L): M

Zinc borate was assigned a score of Moderate for corrosion/irritation as both dermal and ocular irritation have been reported.

- *Dermal*: Contact with skin causes irritation (HSDB 2003).
- *Dermal*: The Primary Irritation Index of zinc borate in rabbits was found to be 0. Therefore, it is not considered to be an irritant or corrosive (U.S. EPA 1991).
- *Ocular*: Contact with eyes causes irritation (HSDB 2003).
- *Ocular*: Zinc borate produced only mild conjunctivitis in albino rabbits in the eye irritation test and is not considered to be an irritant or corrosive (U.S. Borax 1996).
- *Ocular*: Zinc borate was shown to be an eye irritant producing mild conjunctivitis in albino rabbits (U.S. EPA 1991).
- *Inhalation*: Inhalation of dust may irritate nose and throat (HSDB 2003).
- Zinc borates are not skin or eye irritants (no species or doses provided) (EFRA 2006).

Sensitization (Sn) Score (Skin and Respiratory) (H, M or L): L

Because sensitization data were sparse for zinc borate, the structurally similar zinc oxide and boric acid were used as surrogates. Zinc borate was assigned a score of Low for sensitization based on negative sensitization test results in surrogates.

Zinc borate

- *Dermal*: Zinc borate was negative in the guinea pig sensitization test (U.S. Borax 1996).

Zinc oxide

- The skin sensitization potential of zinc oxide (99.69% purity) was investigate in female Dunkin Hartley guinea pigs in two well-performed maximization tests, conducted according to Directive 96/54/EC B.6 and OECD guideline 406. Based on the results of a preliminary study, in the main studies experimental animals (10

in each test) were intradermally injected with a 20% concentration and epidermally exposed to a 50% concentration (i.e. the highest practically feasible concentration). Control animals (5 in each test) were similarly treated, but with vehicle (water) alone. Approximately 24 hours before the epidermal induction exposure, all animals were treated with 10% SDS. Two weeks after the epidermal application, all animals were challenged with a 50% test substance concentration and the vehicle. In the first study, in response to the 50% test substance concentration skin reactions of grade 1 were observed in 4/10 experimental animals 24 hours after the challenge (40% sensitization rate), while no skin reactions were evident in the controls. In contrast, in the second study no skin reactions were evident in the experimental animals (0% sensitization rate), while a skin reaction grade 1 was seen in one control animal. The skin reaction observed in one control animal is probably a sign of non-specific irritation (Van Huygevoort, 1999b1; 1999b2). In a third, well-performed maximization test, conducted according to the same guidelines and with the same experimental design, another analytical grade zinc oxide was tested (Zincweiß Pharma A; purity 99.9%). The only difference with the studies described above was the intradermal induction concentration, which was 2% as for Zincweiß Pharma A this was considered the highest concentration that could reproducibly be injected. In this test, no skin reactions were evident in both experimental and control animals, hence a 0% sensitization rate for Zincweiß Pharma A. White staining of the treated skin by the test substance was observed in some animals 24 and 48 hours after challenge (Van Huygevoort 1999i).

- In a human patch test performed with 100 selected leg-ulcer patients, 11/100 patients gave an allergic reaction with zinc ointment (60% ZnO and 40% sesame oil). However, 14/81 patients gave a positive response when treated with sesame oil alone (Malten and Kuiper 1974). This study does not give any indication for a skin sensitizing potential of zinc oxide in humans. Söderberg et al. (1990) studied the effect of zinc oxide on contact allergy to colophony. With 14 patients with earlier history of moderate patch test reactions to colophony a patch test with 10% ZnO (2.3 mg Zinc/cm²) with and without colophony was performed. No positive response was observed in the 14 patients when only a 10% solution of zinc oxide was used. The addition of zinc oxide to colophony decreased the allergic reaction induced by colophony.
- The data submitted fulfill the base-set requirements for skin sensitization testing. While some studies with guinea pigs produced conflicting results, the weight of evidence does not indicate that zinc oxide is a very potent sensitizing agent in animals, if any. In addition, the results of human patch tests do not indicate that zinc oxide acts as a sensitizing agent in humans, either. Zinc oxide does not have to be classified/labeled for skin sensitization. This is supported by the fact that zinc compounds, especially zinc oxide and zinc distearate, have been used for over decades in a variety of pharmaceutical and cosmetic products (some of them even dermatological preparations against skin irritation) without any such reported effects (ESIS 2008).

<u>Boric acid</u>

- Boric acid and sodium tetraborates are not skin sensitizers in either human and animal studies (Wnorowski 1994a,b,c; Bruze et al.1995).

Systemic/Organ (ST) Toxicity Score (includes organ effects and immunotoxicity) (H, M or L): M

Because systemic toxicity data were sparse for zinc borate, the structurally similar zinc oxide and boric acid were used as surrogates. Zinc borate was assigned a score of Moderate for systemic toxicity based on an oral LOAEL for systemic effects of 81.3 mg ZnO/kg bw.

Zinc borate

- In animal feeding studies, high levels of boric acid displays effects on fertility (rats, mice. dogs) and development (rats, mice, rabbits). High levels of zinc salts do cause adverse effects on fertility and development in animals, but at doses that perturb copper homeostasis resulting in other adverse effects. The doses administered were many times in excess of those which humans would be exposed and therefore the effects would not be seen in humans. A human epidemiology study on workers exposed to boric acid and sodium borates indicated no effect on fertility, while a study in pregnant women taking zinc supplements found no adverse effects. Zinc is an essential element for normal fetal development. Also, there is increasing evidence that boron is nutritionally important and may be essential for mammals (EFRA 2006).

Zinc oxide

- Four groups of ferrets (3-5/group) were given 0, 500, 1,500, or 3,000 mg zinc oxide/kg feed (equivalent to be 0, 81.3, 243.8 or 487.5 mg ZnO/kg bw, respectively. At the highest dose level (487.5 mg ZnO/kg bw) all animals (3) were killed in extremis within 13 days. Macroscopic examination showed pale mucous membranes, dark colored fluid in the stomach, blood in the intestines, orange colored liver and enlarged kidneys showing diffuse necrosis, hemorrhages in the intestine and a severe macrocytic hypochromic anaemia. Histology showed nephrosis and extramedullary hematopoesis in the spleen. At the mid dose level of 243.8 mg ZnO/kg bw, the animals (4) were killed on day 7, 14 and 21 (1/2 in extremis) showing poor condition. Macroscopy showed pale livers with fatty infiltration and enlarged kidneys. Histology was comparable with the highest dose group. The hemogram showed macrocytic hypochromic anaemia, increased reticulocytes and leucocytosis. At the lowest dose level (81.3 mg ZnO/kg bw), the animals (3) were killed on day 48, 138 and 191, respectively. No clinical signs of toxicity or pathological changes were seen, apart from an extramedullary heamatopoesis in the spleen (Straube et al. 1980).
- Ellis et al. (1984) conducted a 14 day and a 49 day feeding study in 3 different breeds of sheep that were receiving feed containing 31 mg Zn^{2+}/kg feed. The sheep received additional amounts of Zn^{2+} (from ZnO) at dose levels of 261 and 731 (14 day study), or 731 and 1,431 mg Zn^{2+}/kg feed (49-day study). No effects were seen after 261 mg Zn^{2+}/kg feed. In all other groups, pancreatic lesions were seen.
- Administration of 240 mg Zinc (as ZnO)/kg bw for 3 times/week during 4 weeks to 42 castrated sheep resulted in an increased incidence of pancreatic lesions (Smith and Embling 1993).

- Male Hartley guinea pigs were exposed to 0, 2.3, 5.9, or 12.1 mg/m^3 of ZnO (as ultra fine particles with an average diameter of 0.05 μm) 3 hours a day for 1, 2, or 3 consecutive nose-only exposures. Three animals from each group were examined after each exposure period; they were sacrificed and lung tissues were microscopically examined, and the pulmonary lavage fluid was also examined. Exposure to 12.1 mg/m^3 increased the number of nucleated cells in lavage fluid. Exposures to 5.9 and 12.1 mg ZnO/m^3 were associated with increased protein, neutrophils, and activities beta glucuronidase, acid phosphatase, alkaline phosphatase, lactate dehydrogenase, and angiotensin-converting enzyme. The increases were dose dependent and were detectable after the second exposure and generally increased after the third exposure. Significant morphologic damage characterized by centriacinar inflammation in the lung was seen at 5.9 and 12.1 mg/m^3. Minimal changes in neutrophils and activities of lactate dehydrogenase and alkaline phosphatase were seen in the pulmonary fluid at the lowest dose level of 2.3 mg/m^3 after 3 exposures but no morphologic changes were observed at this dose level. Based on these results, 2.3 mg ZnO/ m^3 is considered as a marginal LOAEL in this study (Conner et al. 1988).
- Male Hartley guinea pigs were exposed to 6 mg/m^3 of ultra fine ZnO (average diameter of 0.05 μm) for 3 hours a day for 1 to 5 days by nose-only exposure. A control group was included. After each exposure, 3 animals were sacrificed and lung tissues were microscopically examined. After first, second and third exposure 3 additional animals were sacrificed and their pulmonary lavage fluid was examined. ZnO-exposure increased the total cell count, neutrophils, protein, and the enzyme activities of angiotensin converting enzymes, Acid phosphatase, alkaline phosphatase, and β-glucoronidase. Furthermore, a dose-related centriacinar inflammation was seen after second exposure (Conner et al. 1986).
- Male Hartley guinea pigs were exposed to 0, 2.7, or 7 mg ultra fine (0.05 μm in diameter) ZnO/m^3 3 hours a day for 5 days. Lung function measurements were performed every day after exposure in 5-8 animals. After the last exposure the animals were sacrificed. At the highest exposure level, a gradual decrease in total lung capacity (18%) and vital capacity (22%) was seen during the exposure period. At day 4, the carbon monoxide diffusing capacity dropped to below 30% of the control level. Wet-lung weights were increased with 29%, indicating the presence of edema. Exposures up to 2.7 mg ZnO/m^3 did not alter any parameters measured (Lam et al. 1988).
- Male Hartley guinea pigs (73) were exposed (nose-only) 3 hours a day for 6 days to 5 mg ZnO/m^3 (0.05 μm in diameter). A group of 53 animals served as control group. Lung function tests (in 38 animals) were performed and the respiratory tract of the animals was morphologically examined 1, 24, 48 and 72 hours after the last exposure. Furthermore epithelial permeability (5 animals at 1 and 24 hours) and DNA synthesis in epithelial cells (5 animals at 24, 48 and 72 hours) were determined. Vital and functional residual capacity, alveolar volume and carbon monoxide diffusing capacity were all decreased and did not return to normal values 72 hours after the last exposure. Lung weights were elevated due to inflammation, still present at 72 hours after last exposure (Lam et al. 1985).
- 240 Female Wistar rats (80/group) were exposed by inhalation to 15 mg ZnO/m^3 for 1 hour, 4 hours or 8 hours a day for 5 days a week. 20 Animals/group were

sacrificed after 14, 28, 56, and 84 days and their lungs were examined for zinc content. It appeared that the highest daily exposure time resulted in the highest dry lung weights, independent of the duration of the experiment, while the zinc content remained almost constant. The absolute and relative (relative to dried weights of lung tissue) zinc content in the lungs was influenced by the duration of the experiment. After 84 days exposure the zinc content was significantly higher compared to 14 days exposure, independent of the duration of the daily exposure (Dinslage-Schlünz and Rosmanith 1976).

Boric acid

- A number of studies in which rats were fed boric acid or disodium tetraborate decahydrate in their diet or drinking water for periods of 70 - 90 days indicated that the main target organ for toxicity is the testis. As well as testicular atrophy, animals receiving doses of 88 mg B/kg bw/day for 90 days in their diet exhibited weight loss and, at higher doses, rapid respiration, inflamed eyes, swollen paws and desquamation of the skin on the paws (Weir and Fisher 1972; NTP 1987). The main effects observed were on the testis.

Ecotoxicity

Acute Aquatic (AA) Toxicity Score (H, M or L): H

Because acute aquatic toxicity data were limited for zinc borate, the structurally similar zinc oxide and boric acid were used as surrogates. Zinc borate was assigned a score of High for acute aquatic toxicity based on the risk phrases: R50-R53.

- Zinc borates are classified as Dangerous to the Environment, R50/R53, Very toxic to aquatic organisms/May cause long-term effects in the aquatic environment. Zinc borates are considered as 'sparingly soluble salts' based on their toxicity. However, both boron and zinc are essential micronutrients for the healthy growth of plants and other aquatic organisms (EFRA 2006).

Zinc oxide:

- Associated with risk phrases R50, R51, R52, and R53 (ESIS 2008).
- *Algae*: The two tests with the unicelllular alga *Pseudokierchneriella subcapitata* (formerly known as *Selenastrum capricornutum*), in which two different grades of ZnO were tested ("Red seal grade", purity 99.77%, and "EPM-grade", purity 99.37%), resulted in 72-h ErC_{50} values for dissolved zinc of 135 and 136 µg Zn/l, respectively, for endpoint specific growth rate. The 72-h NOErC values for dissolved zinc were 8 and 24 µg/l, respectively (Table 3.3.1: LISEC, 1997; Van Ginneken 1994a). These NOEC values suggest that Red seal-grade ZnO may be somewhat more toxic than EPM-grade ZnO, but because of some differences between the two tests (using either statistics to derive the NOEC or using the lowest test concentration that resulted in less than 10% effect as NOEC; and either measuring dissolved zinc in the stock solution or in the test waters) and the small difference between the NOEC values, a firm conclusion cannot be drawn. Although red-seal grade ZnO and EPM-grade ZnO both have a high purity, the former contains somewhat less impurities (soluble salts) and is somewhat less soluble than the latter (see also footnote 7 below Table 3.3.1). Based on these characteristics, a somewhat lower toxicity could be predicted for Red-seal ZnO

compared to EPM-grade ZnO, which seems to be not in agreement with the above test results. It is noted that similar growth inhibition tests with the same algal species have been conducted with either a soluble zinc compound or with zinc metal powder (see Table 3.3.2.a and Table 3.3.2.d, respectively, in Annex 3.3.2.A of the Risk Assessment Report on Zn metal). These tests and the above tests with ZnO, all using soft to very soft artificial test media, resulted in comparable NOEC values if expressed as dissolved zinc, i.e. NOEC values in the range of 5-50 µg/l, regardless whether a soluble or "insoluble" test compound was used.

- *Invertebrates*: A short-term *Daphnia magna* immobilization test with "EPM-grade" ZnO (purity 99.37%) resulted in a 48-h EC_{50} for dissolved zinc of 1,760 µg/l and a 48-h NOEC for dissolved zinc of 280 µg/l (Table 3.3.1: Van Ginneken 1994b). It is noted that the 48-h NOEC of 280 µg/l from this short-term test is within a factor of 2 of a number of NOEC values (endpoints: survival, reproduction and/or growth) derived in longterm *D. magna* tests in which a soluble zinc salt was used as test compound (see Table 3.3.2.a in Annex 3.3.2.A of the Risk Assessment Report on Zinc metal).
- *Fish*: In a 96-h acute toxicity test with fish *Brachydanio rerio* (test compound "EPM-grade" ZnO, purity 99.37%), no effect was found for dispersed ZnO at 100 mg ZnO/l (limit test), thus the 96-h EC_{50} is >100 mg ZnO/l, nominal concentration, equivalent to >80 mg Zn/l. The actual dissolved zinc concentration in this ZnO dispersion was 4,700 µg Zn/l (Table 3.3.1: Van Woensel 1994b).

Boric acid

- A summary of appropriate acute test results are detailed in Table 14. Eisler (2000) and Dyer (2001) have compiled numerous literature values. The most sensitive tests report that acute effects on fish are in the range of 10-20 mg-B/L although the quality of these studies was rated low (Reliability code 4). The lowest daphnid acute value is 133 mg-B/L. Algal and microbial inhibition studies (Table 15) suggest less toxicity: Selenastrum growth was not affected at 93 mg-B/L and activated sludge respiration showed minimal effects at 683 mg/L boric acid (119 mg-B/L).
- Other results showed substantially higher values (less toxicity) with fish acute values often exceeding 100 mg-B/L. Juveniles and fry appear to be the most sensitive fish life-stage (Hamilton 1995; Hamilton and Buhl 1990).
- Aquatic studies have been used to create species sensitivity distributions (SSD). SSD incorporate all available information into a summary statistic by calculating a designated percentile of the distribution, such as the 5th percentile. Such values indicate a concentration that is predicted to protect 95% of all species (included those not tested) (Cardwell et al. 1993). Dyer et al. (2001) calculated the Acute 5th percentile concentration for aquatic species. Using the procedure of Aldenberg and Slob (1993), the acute 5th percentile SSD concentration is 43 mg-B/L (246 mg-boric acid/L). Using a similar procedure of Stephan et al. (1985) produces a similar value, 46 mg-B/L (263 mg-boric acid/L).

Chronic Aquatic (CA) Toxicity Score (H, M or L): nd

Because chronic aquatic toxicity data were unavailable for zinc borate, the structurally similar zinc oxide and boric acid were used as surrogates. No relevant chronic aquatic toxicity data were identified for zinc borate, zinc oxide, or boric acid.

Zinc borate

- No relevant data were identified.

Zinc oxide

- No relevant chronic aquatic toxicity data were identified for zinc oxide.

Boric acid

- No relevant chronic aquatic toxicity data were identified for boric acid.

Environmental Fate

Persistence (P) Score (vH, H, M, or L): nd

Because persistence data were unavailable for zinc borate, the structurally similar zinc oxide and boric acid were used as surrogates. No relevant persistence data were identified for zinc borate, zinc oxide, or boric acid.

Zinc borate

- No relevant persistence data were identified for zinc borate.

Zinc oxide:

- No relevant persistence data were identified for zinc oxide.

Boric acid:

- No relevant persistence data were identified for boric acid.

Bioaccumulation (B) Score (vH, H, M, or L): L

Zinc borate was assigned a score of Low for bioaccumulation based on professional opinion.

- Zinc borate has a low bioaccumulation potential. Additionally, Firebrake ZB (zinc borate) will undergo hydrolysis in water to form boric acid and zinc hydroxide. Neither of this substances will biomagnify through the food chain (20 Mule Team 2002).

Physical Properties

Explosivity (Ex) Hazard Rating (H, M or L): L

Zinc borate was assigned a score of Low for explosivity as no basis for concern was identified.

- Not explosive (20 Mule Team 2000).

Flammability (F) Hazard Rating (H, M or L): L

Zinc borate was assigned a score of Low for flammability as no basis for concern was identified.

- NFPA rating of 0 assigned for flammability (i.e. zinc borate is not flammable) (Fisher Scientific 2007).

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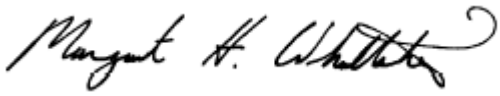

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Exp Key Acute toxicity: oral.001

Administrative Data | Data source | Materials and methods | Results and discussions | Applicant's summary and conclusion

Administrative Data

Purpose flag	key study
Study result type	experimental result
Reliability	2 (reliable with restrictions)
Rationale for reliability incl. deficiencies	Well performed guideline conform non GLP study.

Data source

Reference

Reference type	study report
Year	1975
Report date	1975-03-10

Materials and methods

Test type

standard acute method

Limit test

yes

Test guideline

Qualifier	according to
Guideline	OECD Guideline 401 (Acute Oral Toxicity)
Deviations	yes

Principles of method if other than guideline

only one group of animals has been used
a dose of 15000 mg/kg body weight has been used instead of 2000 mg/kg body weight
only female rodents were used because in prior studies sex-related differences had not been noticed

GLP compliance

no study performed before GLP guidelines

Test materials

Identity of test material same as for substance defined in section 1 (if not read-across)

yes

Details on test material

- Name of test material (as cited in study report): Phosphor rot
- Substance type: element
- Physical state: powder
- Stability under test conditions: stable

Test animals

Species

rat

Strain

Wistar

Sex

	female

Details on test animals and environmental conditions

TEST ANIMALS
- Source: report 131/75
- Weight at study initiation: see table below
- Fasting period before study: 16 hours
- Housing: in plastic cages on wood shavings
- Diet (e.g. ad libitum): Altromin 1324 (Altrogge)
- Water (e.g. ad libitum): ad libitum

Administration / exposure

Route of administration

	oral: gavage

Vehicle

	other: 1% starch mucilage

Details on oral exposure

MAXIMUM DOSE VOLUME APPLIED: 15000 mg/kg body weight

Doses

one dose with 15000 mg/kg body weight

No. of animals per sex per dose

10

Control animals

	no

Details on study design

- Duration of observation period following administration: 14 days (or other?) 14 days
- Frequency of observations and weighing: 7 days
- Necropsy of survivors performed: yes
- Other examinations performed: clinical signs, body weight,organ weights, histopathology, other: clinical signs, body weight, necropsy

Results and discussions

Effect levels

Sex	female
Endpoint	LD50
Effect level	> 15000 mg/kg bw

Mortality

no mortality occured during the study

Clinical signs

no clinical signs have been observed

Body weight

92-104 g (average body weight = 96,6 g)

Gross pathology

No effects

Any other information on results incl. tables

body weight of the rats

Animal no.	sex	dose [mg/kg]	initally body weight	body weight after 7 days	body weight after 14 days
1	female	15000	98	138	160
2	female	15000	90	120	136
3	female	15000	102	144	166
4	female	15000	94	128	150
5	female	15000	94	126	150
6	female	15000	92	126	144
7	female	15000	104	146	172
8	female	15000	96	124	142

9	female	15000	96	138	158
10	female	15000	100	128	144

Applicant's summary and conclusion

Interpretation of results

practically nontoxic

Criteria used for interpretation of results

EU

Conclusions

The LD50 (acute oral) of red phoshorus in female rats is > 15000 mg/kg bw.

Executive summary

After the administration of the highest applicable amount of 15,000 mg red phosphorus
/kg bw, the all animals survived and showed normal behavior during the 14 days observation time.
The trend in body weight of the animals during the observation period is given in the table above. The necropsy of the killed animals at the end of the observation period did not reveal any macroscopically visible changes.
Based on the current results the specific acute oral toxicity could not be determined. The acute oral LD50 for female rats is for sure above 15000 mg/kg body weight.

Exp Supporting Acute toxicity: oral.002

Administrative Data | Data source | Materials and methods | Results and discussions | Applicant's summary and conclusion

Administrative Data

Purpose flag	supporting study
Study result type	experimental result
Study period	1981
Reliability	2 (reliable with restrictions)
Rationale for reliability incl. deficiencies	Scientific sound study analogue to OECD 401 with restricted reporting.

Data source

Reference

Reference type	study report
Year	1981

Materials and methods

Test type

fixed dose procedure

Limit test

yes

Test guideline

Qualifier	equivalent or similar to
Guideline	OECD Guideline 401 (Acute Oral Toxicity)
Deviations	no data

GLP compliance

no study performed before GLP guidelines

Test materials

Identity of test material same as for substance defined in section 1 (if not read-across)

yes

Details on test material

- Name of test material (as cited in study report): oiled red phosphorus Albright and Wilson, LDT. Lot LT 22 RED PHOSPHORUS)
- Substance type: element
- Physical state: solid / powder
- Analytical purity: > 94,6 % +- 1,20 %
- Impurities (identity and concentrations): < 0,0055 % +- 0,0020 % yellow phosphorus
- Composition of test material, percentage of components:approx. 94,6 % total phosphorus, 0,08 % +- 0,010 % mineral oil

Test animals

Species

rat

Strain

Fischer 344

Sex

male/female

Details on test animals and environmental conditions

TEST ANIMALS
- Source: Charles River Breeding Laboratories, Inc. Portage, Michigan
- Age at study initiation: 10 to 13 weeks old
- Weight at study initiation:
first experiment: males: 190 to 240 g body weight and females: 146 to 172 g body weight
second experiment: males: 184 to 210 g body weight and females: 163 to 174 g body weight
- Housing: wired bottom cages
- Diet (e.g. ad libitum): Purina Rat Chow
- Water (e.g. ad libitum): Acified water (pH 2.5)
- Acclimation period: 1 week

ENVIRONMENTAL CONDITIONS
- Temperature (°F): 72° to 76°F
- Humidity (%): 39 to 54 percent relative humidit
- Photoperiod (hrs dark / hrs light): 12h dark / 12h with artificial illumination.

Male and female Fischer 344 (F344) albino rats were obtained from Charles River Breeding Laboratories, Inc. Portage, Michigan, Animals were acclimated to laboratory conditions for 1 week, They were Individually housed In wire- bottom cages, In quarters maintained at temperatures of 72° to 76°F and 39 to 54 percent relative humidity, A 12-hour light cycle was maintained with artificial illumination. Acidified water (pH 2.5) and Purina Rat Chow were provided ad libitum except 18 to 24 hr before treatment when food was withheld. Animals were identified by ear tags.

Administration / exposure

Route of administration

oral: gavage

Vehicle

corn oil

Details on oral exposure

Oiled red phosphorus was suspended in corn oil and administered by oral Intubation at concentration levels to provide 1.0 mL per 100 g body weight.
Male rats weighing between 190 and 240 g and female rats with body weights of 146 to 172 g, 10 to 13 weeks of age were used in the range-finding studies. These studies were performed with two males and two females at each of four dose levels. Three additional male and three female rats were administered the high-dose level (10,000 mg/kg bw) 6 days after the first experiment. To confirm the results of the second treatment with the high-dosage level, an additional 10 male (184 to 210 g body weight) and 10 female (163 to 174 g body weight) rats, 9 to 13 weeks of age, were given this dose. Animals were observed for 14 days following treatment.

Doses

1000, 3160, 6810 and 10000 mg/kg bw

No. of animals per sex per dose

1000, 3160, 6810 mg/kg bw: 2
10000 mg/kg bw: test I: 5; test II: 10

Control animals

no

Details on study design

Please refer to "Details on oral exposure"

Statistics

None

Results and discussions

Preliminary study (if fixed dose study)

No mortality occured with doses of 1000, 3160, 6810 and 10000 mg/kg bw.

Effect levels

Sex	male/female
Endpoint	LD50
Effect level	> 10000 mg/kg bw

Mortality

Intubation of 10000 mg/kg bw red phopphorus to five rats per sex (test I) produced lethalityin one male rat. No additional deaths were observed in this group.
After oral administration to an additional 10 rats per sex (test II) one female died on day 7. This animal may have had an infection.

Clinical signs

10000 mg/kg bw

test I: The body weights of one male and one female at the end of the observation period were lower than their weights before treatment.
test II: no marked toxic effect was observed on body weight although some rats of both sex did not gain weight between days 7 and 14.

Body weight

Please refer to "Clinical signs"

Gross pathology

Necropsy of the dead male (10000 mg/kg bw, test I) revealed gas-filled distended intestines.
The lungs of the dead female (10000 mg7kg bw, test II) were dark red and fluid-filled. The rat had shown dyspnea.

Any other information on results incl. tables

14 days after treatment the results of the range-finding study, employing two rats per sex per dose, suggested that oiled red phosphorus did not produce lethality at doses of 1,000, 3,160, and 6,810 mg/kg (Table 1). Rats of both sexes gained body weight during the 14-day observation period. Intubation of 10,000 mg/kg red phosphorus to five rats per sex (test I) produced lethality in one male rat. Necropsy findings were gas-filled distended intestines. Although no additional deaths were observed in these groups, the body weights of one male and one female at the end of the observation period were lower than their body weights before treatment. Another female lost body weight between days 7 and 14.
Oral administration of the high dose to an additional 10 rats per sex(10000 mg/kg bw, test II), did not produce as marked a toxic effect on body weight although some rats of both sex did not gain weight between days 7 and 14. This reduced body weight gain was most apparent in females. The one female which died on day 7 may have had an infection. The lungs were dark red and fluid-filled, and the rat had shown dyspnea.
Table 1:

Dose (mg/kg)	Mean Body Weight (g)			Deaths					Total	Mortality
	Days after Treatment			Days after Treatment					Deaths/	Treated
	0	7	14	0	1	2 -6	7	8 -14		
Males										
1,000	204	229	247	-	-	-	-	-	0	2
3,160	199	219	233	-	-	-	-	-	0	2
6,810	211	241	264	-	-	-	-	-	0	2
10,000	220	234	226	-	1	-	-	-	1	5
10,000	203	230	241	-	-	-	-	-	0	10
Females										
1,000	154	162	165	-	-	-	-	-	0	2
3,160	151	159	166	-	-	-	-	-	0	2
6,910	156	167	174	-	-	-	-	-	0	2
10,000	162	170	171	-	-	-	-	-	0	5
10,000	166	172	175	-	-	-	1	-	1	10

Applicant's summary and conclusion

Interpretation of results

practically nontoxic

Criteria used for interpretation of results

EU

Conclusions

LD 50 > 10,000 mg/kg body weight

Executive summary

Gastric Intubation of 1,000, 3,610, and 6,810 mg/kg did not produce lethality. After administration of 10,000 mg/kg to five Fischer 344 rats per sex, one male rat died within 24 hour. This experiment was repeated using 10 rats per sex and one female died 7 days after treatment. This animal gave signs of an infection. Other toxic signs at the high-doss level were failure to gain body weight or dose of weight during the 14-day observation period.

BASF

Attachment 4: Registry of Toxic Effects of Chemical Substances (RTECS) entry. Phosphorus (red).

CHEMICAL IDENTIFICATION

RTECS Number	TH3495000
Chemical Name	Phosphorus (red)
CAS Registry Number	7723-14-0
Last Updated	201103
Data Items Cited	40
Molecular Formula	P
Molecular Weight	30.97
Wiswesser Line Notation	.P RED
Compound Descriptor	Agricultural Chemical Human

Synonyms/Trade Names

Phosphorus

HEALTH HAZARD DATA

ACUTE TOXICITY DATA

Type of Test	Route of	Species	Dose	Toxic Effects	Reference

	Exposure	Observed	Data		
LDLo - Lowest published lethal dose	Unreported	Human - man	4412 ug/kg	Details of toxic effects not reported other than lethal dose value	85DCAI "Poisoning; Toxicology, Symptoms, Treatments," 2nd ed., Arena, J.M., Springfield, IL, C.C. Thomas, 1970 Volume (issue)/page/year: 2,73,1970
LD50 - Lethal dose, 50 percent kill	Oral	Rodent - mouse	11.5 mg/kg	Details of toxic effects not reported other than lethal dose value	VCVN5* "Vrednie chemichescie veshestva. Neorganicheskie soedinenia elementov V-VII groopp" (Hazardous substances. Inornanic substances containing V-VII group elements), Bandman A.L. et al., Chimia, 1989. Volume (issue)/page/year: -,58,1993
LD50 - Lethal dose, 50 percent kill	Oral	Rodent - rat	11.5 mg/kg	Details of toxic effects not reported other than lethal dose value	VCVN5* "Vrednie chemichescie veshestva. Neorganicheskie soedinenia elementov V-VII groopp" (Hazardous substances. Inornanic substances containing V-VII group elements), Bandman A.L. et al., Chimia, 1989. Volume (issue)/page/year: -,58,1993
LD50 - Lethal dose, 50 percent kill	Oral	Rodent - rabbit	105 mg/kg	Details of toxic effects not reported other than lethal dose value	VCVN5* "Vrednie chemichescie veshestva. Neorganicheskie soedinenia elementov V-VII groopp" (Hazardous substances. Inornanic substances containing V-VII group elements), Bandman A.L. et al., Chimia, 1989. Volume (issue)/page/year: -,58,1993

LD50 - Lethal dose, 50 percent kill	Oral	Mammal - cat	5 mg/kg	Details of toxic effects not reported other than lethal dose value	VCVN5* "Vrednie chemichescie veshestva. Neorganicheskie soedinenia elementov V-VII groopp" (Hazardous substances. Inornanic substances containing V-VII group elements), Bandman A.L. et al., Chimia, 1989. Volume (issue)/page/year: -,58,1993
LD50 - Lethal dose, 50 percent kill	Oral	Mammal - dog	5 mg/kg	Details of toxic effects not reported other than lethal dose value	VCVN5* "Vrednie chemichescie veshestva. Neorganicheskie soedinenia elementov V-VII groopp" (Hazardous substances. Inornanic substances containing V-VII group elements), Bandman A.L. et al., Chimia, 1989. Volume (issue)/page/year: -,58,1993
LCLo - Lowest published lethal concentration	Inhalation	Rodent - mouse	150 mg/m3	Cardiac - EKG changes not diagnostic of specified effects Liver - fatty liver degeneration Kidney/Ureter/Bladder - other changes	VCVN5* "Vrednie chemichescie veshestva. Neorganicheskie soedinenia elementov V-VII groopp" (Hazardous substances. Inornanic substances containing V-VII group elements), Bandman A.L. et al., Chimia, 1989. Volume (issue)/page/year: -,58,1993
LCLo - Lowest published lethal concentration	Inhalation	Rodent - rat	150 mg/m3	Cardiac - EKG changes not diagnostic of specified effects Liver - fatty liver degeneration Kidney/Ureter/Bladder - other changes	VCVN5* "Vrednie chemichescie veshestva. Neorganicheskie soedinenia elementov V-VII groopp" (Hazardous substances. Inornanic substances containing V-VII group elements), Bandman A.L. et al.,

					Chimia, 1989. Volume (issue)/page/year: -,58,1993
LCLo - Lowest published lethal concentration	Inhalation	Rodent - rabbit	150 mg/m3	Cardiac - EKG changes not diagnostic of specified effects Liver - fatty liver degeneration Kidney/Ureter/Bladder - other changes	VCVN5* "Vrednie chemichescie veshestva. Neorganicheskie soedinenia elementov V-VII groopp" (Hazardous substances. Inornanic substances containing V-VII group elements), Bandman A.L. et al., Chimia, 1989. Volume (issue)/page/year: -,58,1993

OTHER MULTIPLE DOSE TOXICITY DATA

Type of Test	Route of Exposure	Species Observed	Dose Data	Toxic Effects	Reference
TDLo - Lowest published toxic dose	Oral	Rodent - rat	5 mg/kg/10D (intermittent)	Related to Chronic Data - death	VCVN5* "Vrednie chemichescie veshestva. Neorganicheskie soedinenia elementov V-VII groopp" (Hazardous substances. Inornanic substances containing V-VII group elements), Bandman A.L. et al., Chimia, 1989. Volume (issue)/page/year: -,58,1989
TDLo - Lowest published toxic dose	Oral	Rodent - rat	0.12 mg/kg/30D (intermittent)	Blood - other changes Biochemical - Enzyme inhibition, induction, or change in blood or tissue levels - multiple enzyme effects Nutritional and Gross Metabolic - weight loss or decreased weight gain	VCVN5* "Vrednie chemichescie veshestva. Neorganicheskie soedinenia elementov V-VII groopp" (Hazardous substances. Inornanic substances containing V-VII group elements), Bandman A.L. et al., Chimia, 1989. Volume (issue)/page/year: -,58,1989
TDLo - Lowest published toxic dose	Oral	Rodent - rat	5 mg/kg/5D (intermittent)	Liver - hepatitis (hepatocellular necrosis), diffuse Liver - fatty liver degeneration	VCVN5* "Vrednie chemichescie veshestva. Neorganicheskie soedinenia elementov

				Liver - hepatitis, fibrous (cirrhosis, post-necrotic scarring)	V-VII groopp" (Hazardous substances. Inornanic substances containing V-VII group elements), Bandman A.L. et al., Chimia, 1989. Volume (issue)/page/year: -,58,1989
TDLo - Lowest published toxic dose	Oral	Rodent - rat	0.09 mg/kg/26W (intermittent)	Blood - other changes Biochemical - Enzyme inhibition, induction, or change in blood or tissue levels - true cholinesterase Biochemical - Enzyme inhibition, induction, or change in blood or tissue levels - other Enzymes	VCVN5* "Vrednie chemichescie veshestva. Neorganicheskie soedinenia elementov V-VII groopp" (Hazardous substances. Inornanic substances containing V-VII group elements), Bandman A.L. et al., Chimia, 1989. Volume (issue)/page/year: -,59,1989
TDLo - Lowest published toxic dose	Oral	Rodent - rat	0.009 mg/kg/26W (intermittent)	Behavioral - alteration of classical conditioning	VCVN5* "Vrednie chemichescie veshestva. Neorganicheskie soedinenia elementov V-VII groopp" (Hazardous substances. Inornanic substances containing V-VII group elements), Bandman A.L. et al., Chimia, 1989. Volume (issue)/page/year: -,59,1989

REVIEWS

TOXICOLOGY REVIEW	ENTOX* Encyclopedia of Toxicology: Reference Book, Elsevier, 2005 Volume(issue)/page/year: -,624,2005

U.S. STANDARDS AND REGULATIONS

EPA FIFRA 1988 PESTICIDE SUBJECT TO REGISTRATION OR RE-REGISTRATION FEREAC Federal Register. (U.S. Government Printing Office, Supt. of Documents, Washington, DC 20402) V.1- 1936- Volume(issue)/page/year: 54,7740,1989

OCCUPATIONAL EXPOSURE LIMITS

OEL-ARAB Republic of Egypt: TWA 0.1 mg/m3, JAN1993

OEL-HUNGARY: TWA 0.1 mg/m3, STEL 0.1 mg/m3, SEP2000

OEL-JAPAN: OEL 0.1 mg/m3, MAY2009

OEL-NORWAY: TWA 0.1 mg/m3, JAN1999

OEL-THE PHILIPPINES: TWA 0.1 mg/m3, JAN1993

OEL-POLAND: MAC(TWA) 0.3 mg/m3, MAC(STEL) 0.24 mg/m3, JAN1999

OEL-RUSSIA: STEL 0.03 mg/m3, JUN2003

OEL-SWITZERLAND: MAK-W 0.05 mg/m3,KZG-W 0.1 mg/m3, DEC2006

OEL-THAILAND: TWA 0.1 mg/m3, JAN1993

OEL-TURKEY: TWA 0.1 mg/m3, JAN1993

STATUS IN U.S.

EPA TSCA Section 8(b) CHEMICAL INVENTORY

EPA TSCA Section 8(d) unpublished health/safety studies

EPA TSCA Section 8(e) Risk Notification, 8EHQ-0892-9187

On EPA IRIS database

EPA TSCA TEST SUBMISSION (TSCATS) DATA BASE, JANUARY 2001

NIOSH Analytical Method, 1994: Phosphorus, 7905

END OF RECORD

RTECS® is provided quarterly by Accelrys, Inc., and was last updated: **December, 2011**.

BASF

Attachment 5: Registry of Toxic Effects of Chemical Substances (RTECS) entry. Phosphorus (white).

CHEMICAL IDENTIFICATION

RTECS Number	TH3500000
Chemical Name	Phosphorus (white)
CAS Registry Number	7723-14-0
Last Updated	201103
Data Items Cited	77
Molecular Formula	P4
Molecular Weight	123.88
Wiswesser Line Notation	P
Compound Descriptor	Agricultural Chemical Reproductive Effector Human

Synonyms/Trade Names

Bonide blue death rat killer
Common sense cockroach and rat preparations
Fosforo bianco
Gelber phosphor
Phosphore blanc
Phosphorous (white)

Phosphorous yellow
Phosphorus (yellow)
Phosphorus, yellow
Rat-Nip
Tetrafosfor
Tetraphosphor
Weiss phosphor
White phosphorus
Yellow phosphorus

HEALTH HAZARD DATA

ACUTE TOXICITY DATA

Type of Test	Route of Exposure	Species Observed	Dose Data	Toxic Effects	Reference
LDLo - Lowest published lethal dose	Oral	Human - woman	22 mg/kg	Cardiac - cardiomyopathy including infarction	AHJOA2 American Heart Journal. (C.V. Mosby Co., 11830 Westline Industrial Dr., St. Louis, MO 63146) V.1- 1925- Volume (issue)/page/year: 84,139,1972
TDLo - Lowest published toxic dose	Oral	Human - woman	11 mg/kg	Gastrointestinal - hypermotility, diarrhea Gastrointestinal - nausea or vomiting Nutritional and Gross Metabolic - body temperature increase	AJMSA9 American Journal of the Medical Sciences. (Slack Inc., 6900 Grove Rd., Thorofare, NJ 08086) New series: V.1- 1841- Volume (issue)/page/year: 209,223,1944
LDLo - Lowest published lethal dose	Oral	Human - woman	4600 ug/kg	Lungs, Thorax, or Respiration - cyanosis Gastrointestinal - nausea or vomiting Skin and Appendages - sweating	AIMDAP Archives of Internal Medicine. (AMA, 535 N. Dearborn St., Chicago, IL 60610) V.1- 1908- Volume (issue)/page/year: 83,164,1949
TDLo - Lowest published toxic dose	Oral	Human - woman	2600 ug/kg	Behavioral - fluid intake Gastrointestinal - hypermotility, diarrhea Gastrointestinal - nausea or vomiting	NEJMAG New England Journal of Medicine. (Massachusetts Medical Soc., 10 Shattuck St., Boston, MA 02115) V.198- 1928- Volume (issue)/page/year: 232,247,1945
LD50 - Lethal dose, 50 percent kill	Oral	Rodent - rat	3030 ug/kg	Behavioral - somnolence (general depressed activity) Behavioral - food intake (animal) Lungs, Thorax, or	NTIS** National Technical Information Service. (Springfield, VA 22161) Formerly U.S. Clearinghouse for Scientific & Technical Information. Volume

				Respiration - other changes	(issue)/page/year: AD-B011-150
LD50 - Lethal dose, 50 percent kill	Oral	Rodent - mouse	4820 ug/kg	Behavioral - somnolence (general depressed activity) Behavioral - food intake (animal) Lungs, Thorax, or Respiration - other changes	NTIS** National Technical Information Service. (Springfield, VA 22161) Formerly U.S. Clearinghouse for Scientific & Technical Information. Volume (issue)/page/year: AD-B011-150
LDLo - Lowest published lethal dose	Oral	Mammal - dog	10 mg/kg	Details of toxic effects not reported other than lethal dose value	YKYUA6 Yakkyoku. Pharmacy. (Nanzando, 4-1-11, Yushima, Bunkyo-ku, Tokyo, Japan) V.1- 1950- Volume (issue)/page/year: 28,329,1977
LDLo - Lowest published lethal dose	Subcutaneous	Mammal - dog	2 mg/kg	Behavioral - food intake (animal) Cardiac - other changes Liver - fatty liver degeneration	AEXPBL Archiv fuer Experimentelle Pathologie und Pharmakologie. (Leipzig, Ger. Dem. Rep.) V.1-109, 1873-1925. For publisher information, see NSAPCC. Volume (issue)/page/year: 52,173,1905
LDLo - Lowest published lethal dose	Oral	Mammal - cat	4 mg/kg	Details of toxic effects not reported other than lethal dose value	YKYUA6 Yakkyoku. Pharmacy. (Nanzando, 4-1-11, Yushima, Bunkyo-ku, Tokyo, Japan) V.1- 1950- Volume (issue)/page/year: 28,329,1977
LDLo - Lowest published lethal dose	Subcutaneous	Rodent - rabbit	10 mg/kg	Behavioral - muscle weakness Endocrine - hypoglycemia	AEXPBL Archiv fuer Experimentelle Pathologie und Pharmakologie. (Leipzig, Ger. Dem. Rep.) V.1-109, 1873-1925. For publisher information, see NSAPCC. Volume (issue)/page/year: 64,274,1911
LDLo - Lowest published lethal dose	Oral	Mammal - pig	160 mg/kg	Details of toxic effects not reported other than lethal dose value	28ZEAL "Pesticide Index," Frear, E.H., ed., State College, PA, College Science Pub., 1969 Volume (issue)/page/year: 4,321,1969
LDLo - Lowest published lethal dose	Oral	Bird - duck	3 mg/kg	Behavioral - somnolence (general depressed activity) Behavioral - convulsions or	JAPMA8 Journal of the American Pharmaceutical Association, Scientific Edition. (Washington,

				effect on seizure threshold Behavioral - muscle weakness	DC) V.29-49, 1940-60. For publisher information, see JPMSAE. Volume (issue)/page/year: 39,151,1950
LDLo - Lowest published lethal dose	Oral	Mammal - species unspecified	200 mg/kg	Details of toxic effects not reported other than lethal dose value	28ZEAL "Pesticide Index," Frear, E.H., ed., State College, PA, College Science Pub., 1969 Volume (issue)/page/year: 4,321,1969
LD50 - Lethal dose, 50 percent kill	Oral	Bird - duck	6.55 mg/kg	Details of toxic effects not reported other than lethal dose value	HBPTO* Handbook of pesticide toxicology. Robert Krieger ed, Academic press, 2001 Volume (issue)/page/year: 2,1400,2001
LDLo - Lowest published lethal dose	Oral	Human	0.7 mg/kg	Details of toxic effects not reported other than lethal dose value	HBPTO* Handbook of pesticide toxicology. Robert Krieger ed, Academic press, 2001 Volume (issue)/page/year: 2,1402,2001
LDLo - Lowest published lethal dose	Oral	Human - infant	0.4 mg/kg	Details of toxic effects not reported other than lethal dose value	HBPTO* Handbook of pesticide toxicology. Robert Krieger ed, Academic press, 2001 Volume (issue)/page/year: 2,1402,2001
LD90 - Lethal dose	Oral	Human	26 mg/kg	Details of toxic effects not reported other than lethal dose value	HBPTO* Handbook of pesticide toxicology. Robert Krieger ed, Academic press, 2001 Volume (issue)/page/year: 2,1402,2001

OTHER MULTIPLE DOSE TOXICITY DATA

Type of Test	Route of Exposure	Species Observed	Dose Data	Toxic Effects	Reference
TDLo - Lowest published toxic dose	Oral	Rodent - rat	18 mg/kg/4W (intermittent)	Liver - other changes Biochemical - Enzyme inhibition, induction, or change in blood or tissue levels - dehydrogenases Biochemical - Enzyme inhibition, induction, or change in blood or tissue levels - other Enzymes	WDZAEK Weisheng Dulixue Zazhi. Journal of Health Toxicology. (Weisheng Dulixue Zazhi Bianjibu, Dongdaqiao, Chaoyang Menwai, Beijing, Peop. Rep. China) V.1-1987 Volume (issue)/page/year:

					4,206,1990
TDLo - Lowest published toxic dose	Oral	Rodent - rat	12 mg/kg/4D (intermittent)	Liver - hepatitis (hepatocellular necrosis), diffuse Blood - changes in serum composition (e.g. TP, bilirubin, cholesterol) Biochemical - Enzyme inhibition, induction, or change in blood or tissue levels - transaminases	WDZAEK Weisheng Dulixue Zazhi. Journal of Health Toxicology. (Weisheng Dulixue Zazhi Bianjibu, Dongdaqiao, Chaoyang Menwai, Beijing, Peop. Rep. China) V.1-1987 Volume (issue)/page/year: 4,4,1990
TDLo - Lowest published toxic dose	Oral	Rodent - rat	20800 ug/kg/16D (continuous)	Musculoskeletal - other changes	ANREAK Anatomical Record. (Alan R. Liss, Inc., 41 E. 11th St., New York, NY 10003) V.1- 1906/08- Volume (issue)/page/year: 177,15,1973
TDLo - Lowest published toxic dose	Oral	Rodent - rat	85 mg/m3/17W (intermittent)	Liver - fatty liver degeneration Liver - hepatitis, fibrous (cirrhosis, post-necrotic scarring) Biochemical - Enzyme inhibition, induction, or change in blood or tissue levels - cytochrome oxidases (including oxidative phosphorylation)	GTPZAB Gigiena Truda i Professional'nye Zabolevaniya. Labor Hygiene and Occupational Diseases. (V/O Mezhdunarodnaya Kniga, 113095 Moscow, USSR) V.1-36, 1957-1992. For publisher information, see MTPEEI Volume (issue)/page/year: 26(9),17,1982
TDLo - Lowest published toxic dose	Oral	Rodent - rat	91 ug/kg/26W (intermittent)	Behavioral - alteration of classical conditioning Blood - changes in serum composition (e.g. TP, bilirubin, cholesterol) Biochemical - Enzyme inhibition, induction, or change in blood or tissue levels - true cholinesterase	GISAAA Gigiena i Sanitariya. For English translation, see HYSAAV. (V/O Mezhdunarodnaya Kniga, 113095 Moscow, USSR) V.1- 1936- Volume (issue)/page/year: 44(5),74,1979
TDLo - Lowest published toxic dose	Oral	Rodent - rat	11088 ug/kg/22W (continuous)	Nutritional and Gross Metabolic - weight loss or decreased weight gain	JPETAB Journal of Pharmacology and Experimental Therapeutics. (Williams & Wilkins Co., 428

					E. Preston St., Baltimore, MD 21202) V.1- 1909/10- Volume (issue)/page/year: 24,119,1925
TCLo - Lowest published toxic concentration	Inhalation	Rodent - rabbit	160 mg/m3/30M/60D (intermittent)	Blood - pigmented or nucleated red blood cells Blood - changes in erythrocyte (RBC) count Blood - changes in leukocyte (WBC) count	FKIZA4 Fukuoka Igaku Zasshi. (c/o Kyushu Daigaku Igakubu, Tatekasu, Fukuoka-shi, Fukuoka, Japan) V.33- 1940- Volume (issue)/page/year: 46,604,1955
TDLo - Lowest published toxic dose	Oral	Rodent - guinea pig	105 mg/kg/35W (intermittent)	Liver - hepatitis, fibrous (cirrhosis, post-necrotic scarring) Liver - change in gall bladder structure or function Liver - other changes	PSEBAA Proceedings of the Society for Experimental Biology and Medicine. (Academic Press, Inc., 1 E. First St., Duluth, MN 55802) V.1- 1903/04- Volume (issue)/page/year: 67,351,1945
TDLo - Lowest published toxic dose	Oral	Bird - duck	14 mg/kg/14D (intermittent)	Behavioral - somnolence (general depressed activity) Liver - fatty liver degeneration Kidney/Ureter/Bladder - other changes	JAPMA8 Journal of the American Pharmaceutical Association, Scientific Edition. (Washington, DC) V.29-49, 1940-60. For publisher information, see JPMSAE. Volume (issue)/page/year: 39,151,1950

REPRODUCTIVE DATA

Type of Test	Route of Exposure	Species Observed	Dose Data	Sex/Duration	Toxic Effects	Reference
TDLo - Lowest published toxic dose	Oral	Rodent - rat	11 ug/kg	female 1-22 day(s) after conception	Reproductive - Fertility - female fertility index (e.g. # females pregnant per # sperm positive females; # females pregnant per # females	ZDKAA8 Zdravookhranenie Kazakhstana. Public Health of Kazakhstan. (V/O Mezhdunarodnaya Kniga, 113095 Moscow, USSR) V.1- 1941- Volume (issue)/page/year: 36(5),87,1976

mated)
Reproductive - Fertility - post-implantation mortality (e.g. dead and/or resorbed implants per total number of implants)
Reproductive - Fertility - litter size (e.g. # fetuses per litter; measured before birth)

REVIEWS

ACGIH TLV-TWA 0.1 mg/m3	DTLVS* The Threshold Limit Values (TLVs) and Biological Exposure Indices (BEIs) booklet issues by American Conference of Governmental Industrial Hygienists (ACGIH), Cincinnati, OH, 1996 Volume (issue)/page/year: TLV/BEI,2010
TOXICOLOGY REVIEW	NTIS** National Technical Information Service. (Springfield, VA 22161) Formerly U.S. Clearinghouse for Scientific & Technical Information. Volume(issue)/page/year: AD778-725
TOXICOLOGY REVIEW	DIMON* Disease-a Month (Chicago : Year Book Publishers) V. 24- 1978- Volume(issue)/page/year: 39,678,1993
TOXICOLOGY REVIEW	HUTOX* Human Toxicology, Edited by: Jacques Descotes, Elsevier B.V., 1996 Volume(issue)/page/year: -,683,1996
TOXICOLOGY REVIEW	HTOPA* Handbook of Toxicologic Pathology (Second Edition) Edited by: Wanda M. Haschek, Colin G. Rousseaux and Matthew A. Wallig, Elsevier Inc, 2002 Volume(issue)/page/year: 1,595,2002
TOXICOLOGY REVIEW	CCACL* Critical care clinics (Philadelphia : Elsevier Health Sciences Division) V.1- 1985- Volume(issue)/page/year: 21,719,2005
TOXICOLOGY REVIEW	OSMPR* Oral surgery, oral medicine, oral pathology, oral radiology, and endodontics (St. Louis, MO : Mosby-Year Book, Inc.) V.79- 1995- Volume (issue)/page/year: 102,433,2006

U.S. STANDARDS AND REGULATIONS

EPA FIFRA 1988 PESTICIDE SUBJECT TO REGISTRATION OR RE-REGISTRATION
FEREAC Federal Register. (U.S. Government Printing Office, Supt. of Documents, Washington, DC 20402) V.1- 1936- Volume(issue)/page/year: 54,7740,1989

MSHA STANDARD-air:TWA 0.1 mg/m3
DTLVS* The Threshold Limit Values (TLVs) and Biological Exposure Indices (BEIs) booklet issues by American Conference of Governmental Industrial Hygienists (ACGIH), Cincinnati, OH, 1996 Volume(issue)/page/year: 3,210,1971

OSHA PEL (Gen Indu):8H TWA 0.1 mg/m3
CFRGBR Code of Federal Regulations. (U.S. Government Printing Office, Supt. of Documents, Washington, DC 20402) Volume(issue)/page/year: 29,1910.1000,1994

OSHA PEL (Construc):8H TWA 0.1 mg/m3
CFRGBR Code of Federal Regulations. (U.S. Government Printing Office, Supt. of Documents, Washington, DC 20402) Volume(issue)/page/year: 29,1926.55,1994

OSHA PEL (Shipyard):8H TWA 0.1 mg/m3
CFRGBR Code of Federal Regulations. (U.S. Government Printing Office, Supt. of Documents, Washington, DC 20402) Volume(issue)/page/year: 29,1915.1000,1993

OSHA PEL (Fed Cont):8H TWA 0.1 mg/m3
CFRGBR Code of Federal Regulations. (U.S. Government Printing Office, Supt. of Documents, Washington, DC 20402) Volume(issue)/page/year: 41,50-204.50,1994

OCCUPATIONAL EXPOSURE LIMITS

OEL-ARAB Republic of Egypt: TWA 0.1 mg/m3, JAN1993

OEL-AUSTRALIA: TWA 0.1 mg/m3, JUL2008

OEL-BELGIUM: TWA 0.02 ppm (0.1 mg/m3), MAR2002

OEL-DENMARK: TWA 0.1 mg/m3, OCT 2002

OEL-FINLAND: STEL 0.1 mg/m3, SEP2009

OEL-FRANCE: VME 0.1 mg/m3, VLE 0.3 mg/m3, FEB2006

OEL-GERMANY: MAK 0.1 mg/m3 (inhalable), 2005

OEL-HUNGARY: TWA 0.1 mg/m3, STEL 0.1 mg/m3, SEP2000

OEL-JAPAN: OEL 0.1 mg/m3, MAY2009

OEL-KOREA: TWA 0.1 mg/m3, 2006

OEL-MEXICO: TWA 0.1 mg/m3;STEL 0.3 mg/m3, 2004

OEL-THE NETHERLANDS: MAC-TGG 0.1 mg/m3, 2003

OEL-NEW ZEALAND: TWA 0.1 mg/m3, JAN2002

OEL-THE PHILIPPINES: TWA 0.1 mg/m3, JAN1993

OEL-POLAND: MAC(TWA) 0.3 mg/m3, JAN1993

OEL-RUSSIA: TWA 0.03 mg/m3, STEL 0.1 mg/m3, JUN2003

OEL-SWITZERLAND: MAK-W 0.05 mg/m3,KZG-W 0.1 mg/m3, DEC2006

OEL-THAILAND: TWA 0.1 mg/m3, JAN1993

OEL-TURKEY: TWA 0.1 mg/m3, JAN1993

OEL-UNITED KINGDOM: TWA 0.1 mg/m3;STEL 0.3 mg/m3, OCT2007

OEL IN ARGENTINA, BULGARIA, COLOMBIA, JORDAN check ACGIH TLV;

OEL IN SINGAPORE, VIETNAM check ACGIH TLV

NIOSH STANDARDS DEVELOPMENT AND SURVEILLANCE DATA

NIOSH Recommended Exposure Level (Rel)

NIOSH REL TO PHOSPHORUS (YELLOW)-air:10H TWA 0.1 mg/m3

Reference

NIOSH* National Institute of Occupational Safety and Health, U.S. Dept. of Health, Education, and Welfare, Reports and Memoranda. Volume(issue)/page/year: DHHS #92-100,1992

NIOSH Occupational Exposure Survey Data

NOHS - National Occupational Hazard Survey (1974)
Hazard code: M0004
No. of industries: 2
No. of facilities: 38 (estimated)
No. of occupations: 3
No. of employees: 205 (estimated)
NOHS - National Occupational Hazard Survey (1974)
Hazard code: M0005
No. of industries: 1
No. of facilities: 41 (estimated)
No. of occupations: 5
No. of employees: 626 (estimated)
NOHS - National Occupational Hazard Survey (1974)
Hazard code: 81650
No. of industries: 19
No. of facilities: 1187 (estimated)
No. of occupations: 42
No. of employees: 13630 (estimated)
NOHS - National Occupational Hazard Survey (1974)
Hazard code: 81684
No. of industries: 3
No. of facilities: 47 (estimated)
No. of occupations: 4
No. of employees: 261 (estimated)
NOES - National Occupational Exposure Survey (1983)
Hazard code: M0004
No. of industries: 1
No. of facilities: 75 (estimated)
No. of occupations: 1
No. of employees: 675 (estimated)
No. of female employees: 225 (estimated)
NOES - National Occupational Exposure Survey (1983)
Hazard code: M0005
No. of industries: 1
No. of facilities: 6 (estimated)
No. of occupations: 1
No. of employees: 91 (estimated)
No. of female employees: 6 (estimated)
NOES - National Occupational Exposure Survey (1983)

Hazard code: 81650
No. of industries: 104
No. of facilities: 12775 (estimated)
No. of occupations: 88
No. of employees: 208975 (estimated)
No. of female employees: 7598 (estimated)
NOES - National Occupational Exposure Survey (1983)
Hazard code: 81684
No. of industries: 5
No. of facilities: 139 (estimated)
No. of occupations: 10
No. of employees: 2924 (estimated)
No. of female employees: 67 (estimated)

STATUS IN U.S.

ATSDR TOXICOLOGY PROFILE
NTIS** National Technical Information Service. (Springfield, VA 22161) Formerly U.S. Clearinghouse for Scientific & Technical Information. Volume(issue)/page/year: PB/98/101090/AS

EPA TSCA Section 8(b) CHEMICAL INVENTORY

EPA TSCA Section 8(d) unpublished health/safety studies

EPA TSCA Section 8(e) Risk Notification, 8EHQ-0892-9187

On EPA IRIS database

EPA TSCA TEST SUBMISSION (TSCATS) DATA BASE, JANUARY 2001

END OF RECORD

RTECS® is provided quarterly by Accelrys, Inc., and was last updated: **December, 2011**.

Clariant

BU Additives

Preliminary Leaflet

Safety Precautions in Handling Red Phosphorus Powder Grades

General information

Red phosphorus powder grades, unlike yellow phosphorus, are not spontaneously flammable in air. The application of small amounts of energy is however sufficient to ignite them by shock, friction or electrostatic sparking. According to measurements by the *Physikalisch-Technische Bundesanstalt* the low ignition energy of 12.5×10^{-6} Watt sec is sufficient to ignite loose heaped red phosphorus powder; this corresponds to the minimum ignition energy for acetylene-air mixtures. This ignition energy can be produced when electrostatically charged plastics are discharged.

In terms of electrostatic chargeability solids are normally regarded as sufficiently conductive; their surface resistance measured in accordance with VDE 0303, Part 3, §7, is less than 10^9 Ω.

Particularly dangerous is red phosphorus dust finely divided in air, which detonates when ignited, whereas heaped red phosphorus powder burns fairly slowly. Because of the chemical reaction that takes place when red phosphorus powder dusts ignite, the volume of combustion products is likely to be reduced compared to that of the reactants (phosphorus and oxygen) in accordance with the following equation:

$$4\,P_n + 5\,n\,O_2 \xrightarrow{} 2\,n\,P_2O_5 \quad \underset{> 360\ °C}{\overset{< 360\ °C}{\rightleftharpoons}} \quad n\,P_4O_{10}$$

(solid) (gaseous) (solid) (solid)

In the presence of gases that do not take part in the reaction – in air these are nitrogen, carbon dioxide and noble gases – the reaction enthalpy released causes thermally induced dilatation, which results in a rise in pressure locally or in the closed system. However, the resultant explosion pressure is fairly low, although the pressure rise rate of the detonation is fairly high.

Using a *Hartmann* instrument, which is employed to measure dust explosion properties, the following values were obtained.

The particle size of the red phosphorus powder grade used was a maximum of 60 µm:

Dust concentration [g/L]	Maximal explosion pressure [bar]	Pressure rise rate [bar/s]
0.1	2.8	700
0.3	4.0	1200
0.5	3.8	1300
1.0	3.6	1100

The maximum explosion pressure of 4 bar confirms the experience gained in practice that red phosphorus powder dusts do not cause violent explosions. It is essential however not to overlook the fact that on detonation of these dusts a shower of burning particles is produced that can cause dangerous combustion reactions and can set fire instantaneously to flammable substances within reach. Additionally, the initial detonation can cause further dust turbulence, as a result of which a second detonation is triggered.

The ignition temperature of red phosphorus powder grades is between 260 °C and 430 °C, depending on the degree of purity.

The product reacts explosively with oxidizing agents. During decomposition or combustion yellow phosphorus and/or phosphorus pentoxide are formed.

The safe handling of red phosphorus powder grades requires special measures.

The conditions in rooms where industrial amounts of red phosphorus powder grades are processed should in principle be damp. Equally, the red phosphorus powder grades themselves must be processed damp provided the presence of water is not prohibited by subsequent reaction conditions. In such cases the containers must be earthed and any handling carried out under an inert gas blanket. Nitrogen, carbon dioxide and noble gases can be used as inert gases.

The use of an inert gas atmosphere can understandably not prevent ignition and possibly an explosion, if red phosphorus powder grades are mixed with substances that in the mixture with exclusion of air undergo a spontaneous explosive reaction, e.g. thermally splittable oxygen compounds (chlorates, nitrates, peroxides). It is advisable here to damp red phosphorus powder with water, which generally makes the mixing operation harmless.

Red phosphorus powder grades are not toxic. With a LD_{50} of $>$ 15,000 mg/kg body weight they should be classified as "relatively harmless" in accordance with Spector's "Handbook of Toxicology".

Practical handling information

General protective measures
Smoking and any use of fire are prohibited when red phosphorus powder grades are handled.

Rooms in which red phosphorus powder grades are processed or filled must be designed with dust-explosion-proof electrical installations.

If fire breaks out, the most suitable extinguishing agents are water jet, wet sand and fire blankets.

Fire extinguishers that operate under gas pressure are not suitable because they tend to whip up the red phosphorus powder and thus cause the fire to spread.

Areas where fires involving red phosphorus powder have been extinguished should be doused several times with 2% potassium permanganate or with 10% soda or copper sulphate solution to render harmless the toxic and spontaneously flammable yellow phosphorus formed during the fire.

Water-filled tanks or sprinkler systems should be installed in the immediate vicinity of the workplace so that any workwear that catches fire can be extinguished promptly.

In the event of skin burns a doctor must be consulted immediately. Small burns should be treated in the usual manner.
Any adhering traces of phosphorus can be removed with 1 - 5% bicarbonate solution or potassium permanganate solution (pale red).

Protective clothing
It is essential to wear antistatic clothing, especially footwear. Flame-retardant, easily removed gloves, which cover at least the forearm, and a suitable apron should be worn when red phosphorus powder is handled in air. Even better is a flame-retardant protective suit covering the entire body (according DIN EN 531, e.g. Nomex® or Proban® with antistatic finish) when large amounts of red phosphorus powder are handled.

Opening the containers
If possible the containers should be placed on an electrically conductive surface when opened so that any static electricity present is discharged. It is advisable to use an earthing device.

To prevent violent impacts and strong friction no spark-producing metal tools may be used when the lid is opened. It is advisable to use wooden or antistatically treated plastic tools.

Emptying the containers
It is safest to empty containers under an inert gas atmosphere (nitrogen, carbon dioxide, noble gases). If there are no facilities for this, red phosphorus powder can be shovelled in small portions, though dust formation must be prevented at all costs. Here too the principle of avoiding friction and shock and of using only shovels that are not electrostatically chargeable applies.

Destruction of used PE bags
The completely emptied bags must be moistened inside and out with water and rendered inert before being transported. Otherwise there is the risk of ignition or, with large quantities, detonation. The storage time between emptying and destruction must be as short as possible because of the risk of phosphine formation.

Mixing

Red phosphorus powder is best mixed with other powder substances, provided they are not reactive (for further information see under "General information"), in a hermetically sealed container blanketed with inert gas that can be tumbled in a tumbling mixer.

Even when other mixers are used, an absolute inert gas atmosphere must be maintained during mixing.

Incorporation in plastics

Before red phosphorus powder grades are incorporated in plastics it must be ensured that the water content of the polymer is below 0.1% (w/w) if possible, because at temperatures used for plastics processing traces of hydrogen phosphide and phosphoric acids can arise in contact with moisture. It may be necessary to predry the polymers. Effective extraction facilities must be provided at the workplace. When red phosphorus powder grades are premixed with polymer powder or polymer granules the information in the "Mixing" section must be observed. Shear-intensive mixers are not advised.

When red phosphorus powder is metered direct via a separate feed to the polymer melt, the entire metering unit must be rendered inert. The main feed through which the polymer is added must similarly be kept under an inert gas blanket to prevent entrained oxygen from passing from the polymer melt to the phosphorus metering unit.
Extended downtimes of hot plastic processing machinery containing polymers with red phosphorus have to be avoided. Before opening processing machinery for cleaning or maintenance purging with virgin resin is recommended. Otherwise there may be the formation of flames at hot machine parts due to the phosphine generated during the long residence time.

Storage

Red phosphorus powder grades must be kept in a dry place protected from air. Once opened, containers must be resealed and kept tightly closed.

Caution!
Opened containers and those that have become damp should if possible be processed immediately because in a damp atmosphere red phosphorus powder grades slowly liberate hydrogen phosphides, which are highly toxic (MAK value for phosphine (PH_3) 0.1 ppm!) and some of which are spontaneously flammable.

Classification

The classifications applicable to transport can be found in the current safety data sheet.

Edition: January 2010 –
This data sheet replaces all previous issues.

Clariant Produkte (Deutschland) GmbH
BU Additives – BL Flame Retardants
Knapsack Works
Industriestrasse
D-50354 Huerth-Knapsack
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Clariant

Attachment 2: National Industrial Chemicals Notification and Assessment Scheme (NICNAS). Full Public Report, Chemical in Exolit OP 1312.

File No: STD/1168

September 2005

NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)

FULL PUBLIC REPORT

Chemical in Exolit OP 1312

This Assessment has been compiled in accordance with the provisions of the *Industrial Chemicals (Notification and Assessment) Act 1989* (Cwlth) (the Act) and Regulations. This legislation is an Act of the Commonwealth of Australia. The National Industrial Chemicals Notification and Assessment Scheme (NICNAS) is administered by the Department of Health and Ageing, and conducts the risk assessment for public health and occupational health and safety. The assessment of environmental risk is conducted by the Department of the Environment and Heritage.

For the purposes of subsection 78(1) of the Act, this Full Public Report may be inspected at:

Library
Australian Safety and Compensation Council
25 Constitution Avenue
CANBERRA ACT 2600
AUSTRALIA

To arrange an appointment contact the Librarian on TEL + 61 2 6279 1162 or email ascc.library@dewr.gov.au

This Full Public Report is available for viewing and downloading from the NICNAS website or available on request, free of charge, by contacting NICNAS. For requests and enquiries please contact the NICNAS Administration Coordinator at:

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Director
NICNAS

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FULL PUBLIC REPORT

Chemical in Exolit OP 1312

1. APPLICANT AND NOTIFICATION DETAILS

APPLICANT(S)
Clariant (Australia) Pty Ltd, ABN: 30 069 435 552
675 Warrigal Road
Chadstone, Vic 3148

NOTIFICATION CATEGORY
Standard: Chemical other than polymer (more than 1 tonne per year).

EXEMPT INFORMATION (SECTION 75 OF THE ACT)
Data items and details claimed exempt from publication:
Chemical Name
Other Names
CAS No.
Molecular and Structural Formula
Molecular Weight
Spectral Data
Purity
Non-Hazardous Impurities
Hazardous Imputities
Use Details
Import Volume
Identity of Manufacturing Site

VARIATION OF DATA REQUIREMENTS (SECTION 24 OF THE ACT)
Variation to the schedule of data requirements is claimed as follows:

Adsorption/ desorption
Acute inhalation toxicity

PREVIOUS NOTIFICATION IN AUSTRALIA BY APPLICANT(S)
Not applicable

NOTIFICATION IN OTHER COUNTRIES
Korean Inventory
USA
Japan

2. IDENTITY OF CHEMICAL

MARKETING NAME(S)
Exolit OP 1312 (contains the notified chemical at > 60%).

3. COMPOSITION

DEGREE OF PURITY
High

NON HAZARDOUS IMPURITIES/RESIDUAL MONOMERS (> 1% by weight)

One non-hazardous impurity at < 5%.

ADDITIVES/ADJUVANTS
None

4. INTRODUCTION AND USE INFORMATION

MODE OF INTRODUCTION OF NOTIFIED CHEMICAL (100%) OVER NEXT 5 YEARS
The notified chemical is to be imported as a component of the flame retardant product Exolit OP 1312. The manufacture of the notified chemical and its formulation into Exolit OP 1312 will not occur in Australia.

MAXIMUM INTRODUCTION VOLUME OF NOTIFIED CHEMICAL (100%) OVER NEXT 5 YEARS

Year	*1*	*2*	*3*	*4*	*5*
Tonnes	<1000	<1000	<1000	<1000	<1000

USE
Flame retardant for plastic material for the manufacture of electrical components and furniture.

5. PROCESS AND RELEASE INFORMATION

5.1. Distribution, transport and storage

PORT OF ENTRY
Sydney or Melbourne.

IDENTITY OF MANUFACTURER/RECIPIENTS
Clariant (Australia) Pty Ltd
675 Warrigal Road
Chadstone Vic 3148

TRANSPORTATION AND PACKAGING
Exolit OP 1312 will be imported in 25 kg cardboard boxes with polyethylene liners and transported by road to the warehouses for storage until required or directly to the end-user.

The notified chemical is not classified as a dangerous good. However, the imported product Exolit OP 1312 is classified as a dangerous good (Class 9, Environmentally hazardous substance, solid).

5.2. Operation description

Batching and Extruding
The bags (25 kg) of powdered product containing the notified chemical will be transported as required from the warehouse to the production area by forklift or manually. At the plant the powder containing the notified chemical is either weighed or added to a "loss-in weight" feeder by manually cutting open the bags or by manually scooping or pouring the powder into an enclosed and automated batching machine. An enclosed suction system may also be used to transfer powder to a drying unit and then automatically to the "loss-in weight" batch feeder. This involves inserting a large transfer tube into the bag of product containing the notified chemical. The powder is subsequently automatically suctioned to a hopper for blending with other additives. The resultant formulation is transferred automatically to a master batch extruder which is heated to the melting point of the components, and produces pelletised plastic containing 10 – < 30% of the notified chemical. The pellets are automatically packaged into 25 kg plastic bags or 500 kg bulk bags or boxes.

Moulding
The 25 kg bags or 500 kg bulk bags or boxes of reformulated pellets containing the notified chemical

(at 10 – < 30%) will be transported as required from the warehouse to the moulding plants. At the plant the pellets containing the notified chemical is either weighed or added to a "loss-in weight" feeder by manually cutting open the bags or by manually scooping or pouring into a hopper. Material from the hopper is automatically fed into the heated injection unit. The injection unit moulds the article into the desired shape. As soon as the plastic cools to a solid state, the mould opens and the finished solid plastic article is ejected from the press. The moulded plastic article can be moved manually or may be an automated production line. Purged plastic material is recycled.

5.3. Occupational exposure

Number and Category of Workers

Category of Worker	*Number*	*Exposure Duration*	*Exposure Frequency*
Transport	unknown	unknown	<100 days/year
Warehouse and Storage personnel	8	1 hour per day	100 days per year
Production operators (Weighing, loading, packing pellets and cleaning)	20	4 hours per day	100 days per year
Production supervisors (Weighing, loading, packing pellets and cleaning)	4	4 hours per day	100 days per year
Quality control personnel	4	4 hours per day	100 days per year

Exposure Details

Transport and warehousing

Transport, warehouse and stores personnel will wear protective equipment (overalls/ industrial clothing and gloves as appropriate) when receiving and handling consignments of the imported product containing the notified chemical (up to 100% notified chemical). The product will be handled in the warehouse by forklift handling of pallets or manual handling of individual packages. During transport and warehousing, workers are unlikely to be exposed to the notified chemical except when packaging is accidentally breached.

Batching and Extruding

The main routes of exposure to the notified chemical (up to 100% notified chemical) are dermal and accidental ocular and inhalation exposure during weighing and adding the imported powdered product to the automated batching and pellet-extruding machine.

Plant operators are involved in opening the imported packages containing the notified chemical and operating the suction hose which transfers the powder into the fully automated and enclosed batching machine which formulates and extrudes pellets (containing <30% notified chemical). It is possible that dermal, inhalation and accidental ocular exposure to the notified chemical by means of spillages may occur during transfer operations.

It is possible that dermal and accidental ocular and inhalation exposure may occur if manual intervention is required during the automated transfer/suction operations. It is possible that dermal exposure to pellets containing the notified chemical may occur if manual intervention is required during the automated packaging operation or the pellet packages are accidentally breached. Production operators and supervisors will have intermittent dermal exposure to the notified chemical when cleaning the equipment in general. Quality control personnel will have intermittent dermal exposure when sampling batches of the extruded pellets containing the notified chemical.

All workers involved in handling the imported product and extruded pellets will wear personal protective equipment (PPE) such as safety glasses, gloves, protective clothing and dust masks, if necessary. The batching and extruding operations occur under local exhaust ventilation (LVE). All production operators and supervisors are trained in the appropriate operational procedures and precautions.

Moulding

The main routes of exposure to the product containing the notified chemical (<30%) are dermal and accidental ocular and inhalation exposure during weighing and adding the reformulated pelleted product to the hopper. Workers may also be exposed when handling finished moulded articles.

Disposal
Workers may be involved in disposal of waste pelletised plastic or moulded plastic products.

5.4. Release

RELEASE OF CHEMICAL AT SITE
There will be no release in Australia due to manufacture as the notified chemical will not be manufactured here.

Release to the environment during shipping, transport and warehousing will only occur through accidental spills or leaks of the polyethylene bag container. This is expected to be minor due to the packaging of the material.

RELEASE OF CHEMICAL FROM USE
There will be some residual powder left in the empty import bags. This is estimated to be less than 0.2% of the annual import volume (ie less than 2 tonnes annually). Empty bags and any residuals will be disposed of to regulated landfill.

During the extrusion process to incorporate the notified chemical into plastic grades, some waste may be generated by spillage of powder prior to incorporation into the polymer. This waste (up to 0.1% or 1 tonne of the chemical) will be collected and consigned to waste.

The process equipment will not be washed between batches. In each batch the first lot of product is discarded. This discarded material, along with any other out of specification product or off cuts will be collected and either disposed of or recycled, if possible. Any spilt material will be collected and placed into sealable containers ready for disposal.

In the end product the notified chemical is incorporated in an inert matrix and will not be released to the environment.

5.5. Disposal

All the solid wastes generated containing the notified chemical will either be disposed of to landfill. In landfill the notified chemical within the plastic matrix will not be mobile and will slowly under go abiotic and biotic degradation.

5.6. Public exposure

No manufacture of the notified chemical will take place in Australia. The chemical will only be imported as a component of Exolit OP 1312. The product will not be available for use by the general public.

This product will be used industrially for preparation of flame retardant grades of products containing the notified chemical. The industrial products will be used in production of articles in which the notified chemical is bound in the polymer system.

Plastic materials containing the notified chemical are expected to be used in the moulding of electrical components and in moulding of furniture designed for public use. The notified chemical will be bound in articles at a level of <30% based on weight of the article. Members of the public will not routinely be exposed to finished moulded articles. Electrical components will not be handled by the public. The furniture components will form part of the support structure and will not be present in normal accessible places of public contact.

The potential for exposure of the general public to Exolit OP 1312 during normal industrial storage, handling, transportation and manufacturing processes will be minimal. Only in extreme cases of inappropriate handling or accidents during transportation would there be any likelihood of the new chemical being released from the packaging and the public being exposed or contamination of the environment occurring. During normal use of plastics containing the notified chemical public exposure would be minimal.

6. PHYSICAL AND CHEMICAL PROPERTIES

Appearance at 20°C and 101.3 kPa White, odourless powder

Melting Point/Freezing Point > 400°C

METHOD EC Directive 92/69/EEC A.1 Melting/Freezing Temperature.
Remarks Determined by differential scanning calorimetry.

In the temperature range 25–400°C no melting point of the notified chemical was observed.
TEST FACILITY HR & T Analytical Technologies (1998a)

Density 1200 kg/m^3 at 4°C

METHOD EC Directive 92/69/EEC A.3 Relative Density.
Remarks Determined by air comparison pycnometer.
TEST FACILITY HR & T Analytical Technologies (1998b)

Vapour Pressure Test not conducted.

Remarks The notified chemical is a salt and as such would be expected to have a very low vapour pressure, which is supported by DTA/TG investigations which show no weight loss even at updated temperatures.

Water Solubility < 1 mg/L at 20°C

METHOD EC Directive 92/69/EEC A.6 Water Solubility.
Remarks Determined by visual estimate using the shake flask method. At the above level there was still undissolved material present. The notified chemical is very slightly soluble (Mensink *et al.* 1995)
TEST FACILITY HR & T Analytical Technologies (1998c)

Hydrolysis as a Function of pH Not possible to determine.

METHOD EC Directive 92/69/EEC C.7 Degradation: Abiotic Degradation: Hydrolysis as a Function of pH.
Remarks Determination of the rate of hydrolysis was not possible due to the insolubility of the notified chemical in water, organic solvents and buffers. However, the ready biodegradability study reports complete hydrolysis occurred in a stability test within 24 h at pH 4.5. The process that occurred in the stability test is actually dissociation.
TEST FACILITY HR & T Analytical Technologies (1998d)

Partition Coefficient (n-octanol/water) Not possible to determine.

METHOD EC Directive 92/69/EEC A.8 Partition Coefficient.
Remarks Due to the insolubility of the notified chemical in water, organic solvents (solubility in octanol <15.4 mg/L) and buffers neither the HPLC Method or Flask Method could be used to determine the partition coefficient.
TEST FACILITY HR & T Analytical Technologies (1998e)

Adsorption/Desorption Not determined

Remarks The low water solubility of the notified chemical indicates it would partition to soil and sediment.

Particle Size 2 – 40 µm (D_{50})

METHOD OECD TG 110 Particle Size Distribution/Fibre Length and Diameter Distributions.

Range (µm)	*Mass (%)*
<3	10
3-6	20
7-10	10
11-21	30
22-34	20
35-88	10

Remarks Respirable fraction 40% < 10 µm
Inhalable fraction 60% < 100 µm
TEST FACILITY Clariant (1998)

Flash Point Not determined.

Remarks Test not conducted because the notified chemical is a solid.

Flammability Limits The notified chemical could not be ignited with a flame.

METHOD EC Directive 92/69/EEC A.10 Flammability (Solids).
Remarks None.
TEST FACILITY HR & T Analytical Technologies (1998f)

Autoignition Temperature No self-ignition was noted up to a temperature of 402ºC.

METHOD 92/69/EEC A.16 Relative Self-Ignition Temperature for Solids.
Remarks None.
TEST FACILITY HR & T Analytical Technologies (1998g)

Explosive Properties As no exothermic effect occurred up to 400ºC it was concluded no hazard or explosive properties exists for the notified chemical.

METHOD EC Directive 92/69/EEC A.14 Explosive Properties.
Remarks A negative result is predicted on structural grounds.
TEST FACILITY HR & T Analytical Technologies (1998h)

Reactivity Not expected to be reactive under normal environmental conditions.

Dust Explosivity The product may cause dust explosions, lowest ignition energy 13 mJ

METHOD Unknown
Remarks Statement from manufacturer, Clariant GmbH. No report available.
TEST FACILITY Unknown

7. TOXICOLOGICAL INVESTIGATIONS

Endpoint and Result	*Assessment Conclusion*
Rat, acute oral LD50 > 2000 mg/kg bw	low toxicity
Rat, acute dermal LD50 > 2000 mg/kg bw	low toxicity
Rabbit, skin irritation	non-irritating
Rabbit, eye irritation	slightly irritating
Guinea pig, skin sensitisation – adjuvant test	no evidence of sensitisation
Rat, repeat dose oral toxicity – 28 days.	NOAEL = 1000 mg/kg bw
Genotoxicity – bacterial reverse mutation	non mutagenic
Genotoxicity – in vitro chromosomal aberrations in Chinese Hamster V79 cells	non genotoxic

7.1. Acute toxicity – oral

TEST SUBSTANCE — Notified chemical

METHOD — OECD TG 401 Acute Oral Toxicity.
EC Directive 92/69/EEC B.1 Acute Toxicity (Oral).

Species/Strain	Rat/HSD: Sprague Dawley
Vehicle	Sesame oil DAB 10 (20% suspension)
Remarks - Method	No significant protocol deviations

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Mortality*
1	5 males	2000	0/5
2	5 females	2000	0/5

LD50	> 2000 mg/kg bw
Signs of Toxicity	None.
Effects in Organs	No adverse macroscopic observations at necropsy.
Remarks - Results	There were no deaths or notified chemical related clinical signs or remarkable body weight changes during the study period.

CONCLUSION — The notified chemical is of low toxicity via the oral route.

TEST FACILITY — Hoechst Marion Roussell (1998a)

7.2. Acute toxicity – dermal

TEST SUBSTANCE — Notified chemical.

METHOD — OECD TG 402 Acute Dermal Toxicity.
EC Directive 92/69/EEC B.3 Acute Toxicity (Dermal).

Species/Strain	Rat/ HSD:Sprague Dawley SD
Vehicle	Sesame oil (Oil sesami DAB 10)
Type of dressing	Occlusive.
Remarks - Method	No significant protocol deviations.

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw*	*Mortality*
1	5	2000	0/5
2	5	2000	0/5

LD50	> 2000 mg/kg bw
Signs of Toxicity - Local	There were no notified chemical-related dermal reactions.
Signs of Toxicity - Systemic	There were no notified chemical-related dermal reactions.
Effects in Organs	No abnormalities were observed upon macroscopic examination at the end of the study.
Remarks - Results	There were no deaths or notified chemical related clinical signs or remarkable body weight changes during the study period. The skin of the animals showed no signs of irritation.

CONCLUSION The notified chemical is of low toxicity via the dermal route.

TEST FACILITY Hoechst Marion Roussell (1998b)

7.3. Acute toxicity – inhalation

Remarks Test not conducted

7.4. Irritation – skin
7.4.1 Study 1

TEST SUBSTANCE Notified chemical.

METHOD OECD TG 404 Acute Dermal Irritation/Corrosion.
EC Directive 92/69/EEC B.4 Acute Toxicity (Skin Irritation).

Species/Strain	Rabbit/New Zealand albino White
Number of Animals	3
Vehicle	Polyethylene glycol
Observation Period	72 h
Type of Dressing	Semi-occlusive.
Remarks - Method	No significant protocol deviations.

RESULTS

Lesion	*Mean Score* Animal No.*			*Maximum Value*	*Maximum Duration of Any Effect*	*Maximum Value at End of Observation Period*
	1	2	3			
Erythema/Eschar	0	0	0	0	-	0
Oedema	0	0	0		-	0

*Calculated on the basis of the scores at 24, 48, and 72 hours for EACH animal.

Remarks - Results There were no deaths or test substance related clinical signs or remarkable body weight changes during the study period. There were no dermal reactions.

CONCLUSION The notified chemical is non-irritating to the skin.

TEST FACILITY Hoechst Marion Roussell (1997a)

7.4.2 Study 2

TEST SUBSTANCE Notified chemical.

METHOD OECD TG 404 Acute Dermal Irritation/Corrosion.
EC Directive 92/69/EEC B.4 Acute Toxicity (Skin Irritation).
US EPA OPPTS 870.2500, Health Effects Test Guidelines: Acute Dermal Irritation.

Species/Strain	Rabbit/New Zealand albino White
Number of Animals	3
Vehicle	Deionised water.
Observation Period	72 h

Type of Dressing	Semi-occlusive.
Remarks - Method	No significant protocol deviations.

RESULTS

Lesion	*Mean Score* Animal No.*			*Maximum Value*	*Maximum Duration of Any Effect*	*Maximum Value at End of Observation Period*
	1	2	3			
Erythema/Eschar	0	0	0	0	-	0
Oedema	0	0	0		-	0

*Calculated on the basis of the scores at 24, 48, and 72 hours for EACH animal.

Remarks - Results	None.

CONCLUSION The notified chemical is non-irritating to the skin.

TEST FACILITY Aventis Pharma (2003a)

7.5. Irritation – eye

7.5.1 Study 1

TEST SUBSTANCE Notified chemical.

METHOD OECD TG 405 Acute Eye Irritation/Corrosion.
EC Directive 92/69/EEC B.5 Acute Toxicity (Eye Irritation).

Species/Strain	Rabbit/New Zealand White
Number of Animals	3
Observation Period	72 h
Remarks - Method	No significant protocol deviations.

RESULTS

Lesion	*Mean Score* Animal No.*			*Maximum Value*	*Maximum Duration of Any Effect*	*Maximum Value at End of Observation Period*
	1	2	3			
Conjunctiva: redness	1.3	1.0	1.0	3	2 days	0
Conjunctiva: chemosis	0.3	0.3	0.3	2	1 day	0
Conjunctiva: discharge	0.3	0	0.3	1	1 day	0
Corneal opacity	0.3	0	0	1	1 day	0
Iridial inflammation	0.3	0	0	1	1 day	0

*Calculated on the basis of the scores at 24, 48, and 72 hours for EACH animal.

Remarks - Results	One hour up to two days after administration the conjunctivae of the animals showed injected blood vessels up to a deeper crimson red colour. One hour up to one day after administration slight swelling up to obvious swelling were observed. One day after administration the cornea of one animal showed scattered or diffuse areas of opacity and the iris was reddened. Additionally, clear-colourless eye discharge occurred one hour after administration. Three days after administration all signs of irritation were reversed.

CONCLUSION The notified chemical is slightly irritating to the eye.

TEST FACILITY Hoechst Marion Roussell (1997b)

7.5.2 Study 2

TEST SUBSTANCE Notified chemical.

METHOD OECD TG 405 Acute Eye Irritation/Corrosion.

EC Directive 92/69/EEC B.5 Acute Toxicity (Eye Irritation).
US EPA OPPTS 870.2400 Health Effects Test Guidelines: Acute Eye Irritation.

Species/Strain: Rabbit/New Zealand White
Number of Animals: 3
Observation Period: 72 h
Remarks - Method: No significant protocol deviations.

RESULTS

Lesion	*Mean Score* Animal No.*			*Maximum Value*	*Maximum Duration of Any Effect*	*Maximum Value at End of Observation Period*
	1	2	3			
Conjunctiva: redness	0.3	0	0	2	1 day	0
Conjunctiva: chemosis	0.3	0	0	1	1 day	0
Conjunctiva: discharge	0	0	0	1	1 hour	0
Corneal opacity	0	0	0	0		0
Iridial inflammation	0	0	0	0		0

*Calculated on the basis of the scores at 24, 48, and 72 hours for EACH animal.

Remarks - Results: None.

CONCLUSION: The notified chemical is slightly irritating to the eye.

TEST FACILITY: Aventis Pharma (2003b)

7.6. Skin sensitisation

TEST SUBSTANCE: Notified chemical.

METHOD: OECD TG 406 Skin Sensitisation - Magnusson and Kligman.
EC Directive 96/54/EC B.6 Skin Sensitisation - Magnusson and Kligman.

Species/Strain: Guinea pig/Pirbright-White females

PRELIMINARY STUDY: Maximum Non-irritating Concentration:
intradermal: Freund's Complete Adjuvant by itself caused severe irritation
topical: 25% (w/v)

MAIN STUDY

Number of Animals: Test Group: 10 Control Group: 5

INDUCTION PHASE: Induction Concentration:
intradermal: 5% (w/v in sesame oil (Oleum sesami DAB 10)
topical: 25% (w/v) in sesame oil (Oleum sesami DAB 10)

Signs of Irritation: Intradermal injection: The intradermal injections with Freund's Complete Adjuvant (with and without notified chemical) caused severe erythema and oedema as well as indurations and encrustations. The administration sites treated with notified chemical in Oleum sesami DAB 10 showed slight erythema and oedema. Intradermal injections of the vehicle alone exhibited no signs of irritation.

Topical Induction: After removal of the patches at Day 10, severe erythema and oedema, indurated, scabbed and encrusted skin as well as necrosis was observed at the sites previously treated with Freund's Complete Adjuvant. The administration of the notified chemical or vehicle alone exhibited no signs of irritation.

CHALLENGE PHASE

1st challenge: topical: 25% (w/v)

Remarks - Method: No significant protocol deviations.

RESULTS: No dermal reactions were seen in either the control or the test groups at

	24 or 48 hours after patch removal.
Remarks - Results	None.
CONCLUSION	There was no evidence of reactions indicative of skin sensitisation to the notified chemical under the conditions of the test.
TEST FACILITY	Hoechst Marion Roussell (1998c)

7.7. Repeat dose toxicity

TEST SUBSTANCE	Notified chemical.
Method	OECD TG 407 Repeated Dose 28-day Oral Toxicity Study in Rodents. EC DIRECTIVE 96/54/EC B.7 REPEATED DOSE (28 DAYS) TOXICITY (ORAL).
Species/Strain	Rat/Wistar
Route of Administration	Oral - gavage
Exposure Information	Total exposure days: 28 days; Dose regimen: 7 days per week.
Vehicle	Deionised water.
Remarks – Method	No protocol deviations.

RESULTS

Group	*Number and Sex of Animals*	*Dose mg/kg bw/day*	*Mortality*
I (control)	5/sex	0	0/10
II (low dose)	"	62.5	1/10
III (mid dose)	"	250	0/10
IV (high dose)	"	1000	0/10

Mortality and Time to Death

One female of the low dose group died on day 3 from a technical error.

Clinical Observations

High dose males exhibited pultaceous faeces on day 24. Body weights and body weight gain were unaffected by treatment.

Laboratory Findings – Clinical Chemistry, Haematology, Urinalysis

High dose females exhibited a decreased mean cell volume but other red blood cell parameters were unaffected. High dose females also exhibited increased leukocyte count but it was within the normal physiological range. High dose males exhibited increased chloride and high dose females exhibited increased sodium, and decreased glucose and alanine aminotransferase. All clinical chemistry observations were within the normal physiological range. No treatment-related urinalysis changes were noted.

Effects in Organs

High dose males exhibited increased relative liver weights and high dose females increased relative adrenal weights but the changes were within the normal physiological range. No macroscopic or microscopic effects were observed.

Remarks – Results

None.

CONCLUSION

In conclusion, the notified chemical caused no adverse effects when administered 28 times during 29 days at the dose level of 1000 mg/kg body weight per day. The death of 1 female animal of the low dose group on day 3 of the study was due to technical error. The occurrence of pultaceous faeces in male animals of the high dose group on day 24 of the study is not considered to be of toxicological relevance.

The "No Observed Adverse Effect Level" (NOAEL) is 1000 mg/kg body weight per day based on no adverse effects occurring at this dose level and the NOEL is 250 mg/kg bw/day.

TEST FACILITY Hoechst Marion Roussell (1998d)

7.8. Genotoxicity – bacteria

TEST SUBSTANCE Notified chemical.

METHOD OECD TG 471 Bacterial Reverse Mutation Test.
EC Directive 2000/32/EC B.13/14 Mutagenicity – Reverse Mutation Test using Bacteria.
Plate incorporation procedure.

Species/Strain	*S. typhimurium*:, TA1535, TA1537, TA100, TA98
Metabolic Activation System	Aroclor 1254-induced rat liver S9 fraction.
Concentration Range in Main Test	a) With metabolic activation: 4–5000 µg/plate b) Without metabolic activation: 4–5000 µg/plate
Vehicle	Dimethyl Sulfoxide
Remarks - Method	Visible precipitation of the notified chemical was observed at 500 µg/plate and above.

RESULTS

Metabolic Activation	*Test Substance Concentration (µg/plate) Resulting in:*			
	Cytotoxicity in Preliminary Test	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent				
Test 1	No toxicity observed	No toxicity observed	500, 2500, 5000	None
Test 2	No toxicity observed	No toxicity observed	500, 2500, 5000	None
Present				
Test 1	No toxicity observed	No toxicity observed	500, 2500, 5000	None
Test 2	No toxicity observed	No toxicity observed	500, 2500, 5000	None

Remarks - Results Concurrent positive controls demonstrated the sensitivity of the assay and the metabolising activity of the liver preparations. Negative controls were within historical limits.

CONCLUSION The notified chemical was not mutagenic to bacteria under the conditions of the test.

TEST FACILITY Hoechst Marion Roussell (1998e)

7.9. Genotoxicity – in vitro

TEST SUBSTANCE Notified chemical.

METHOD OECD TG 473 In vitro Mammalian Chromosome Aberration Test.
EC Directive 2000/32/EC B.10 Mutagenicity - In vitro Mammalian Chromosome Aberration Test.

Cell Type/Cell Line	Chinese Hamster lung fibroblasts Cell line V79
Metabolic Activation System	Aroclor 1254-induced rat liver S9 fraction.
Vehicle	Suspended in Na_2HPO_4 (0.2 M) and NaH_2PO_4 (0.2 M)
Remarks - Method	None.

Metabolic Activation	*Test Substance Concentration (µg/mL)*	*Exposure Period*	*Harvest Time*
Absent			
Test 1	1.0, 7.8*, 10, 25*, 50, 78*, 100, 250, 500, 700	3 h	20
Test 2	1.0, 7.8*, 10, 25*, 50, 78*, 100, 250, 500, 700	3 h	20
Present			

Test 1 Test 2	1.0, 7.8*, 10, 25*, 50, 78*, 100, 250, 500, 700	20 h	20

*Cultures selected for metaphase analysis.

RESULTS

Evaluation of higher dose levels (250 and 780 µg/mL) was not possible because of heavy precipitation of the test compound on the slides.

Metabolic Activation	*Test Substance Concentration (µg/mL) Resulting in:*			
	Cytotoxicity in Preliminary Test	*Cytotoxicity in Main Test*	*Precipitation*	*Genotoxic Effect*
Absent				
Test 1	None	None	None	None
Test 2	250, 500, 780	None	250, 500, 780	None
Present				
Test 1	None	None	None	None
Test 2	None	None	None	

Remarks - Results

Cytotoxicity was not observed at any test concentration. No statistically or biologically significant increases in the percentage of aberrant cells above the vehicle control levels, were recorded for any cultures treated with the notified chemical in either the presence or absence of metabolic activation. Positive controls confirmed the sensitivity of the test system.

CONCLUSION

The notified chemical was not clastogenic to Chinese Hamster V79 cells treated in vitro under the conditions of the test.

TEST FACILITY

Hoechst Marion Roussell (1998f)

8. ENVIRONMENT

8.1. Environmental fate

8.1.1. Ready biodegradability

TEST SUBSTANCE	Notified substance
METHOD	OECD TG 301 C Ready Biodegradability: Modified MITI Test (I). Method of testing the biodegradability of chemical substances by micro-organisms, in Testing methods for new chemicals substances, July 13, 1974, No 5 Planning and Coordination Bureau, Environment Agency.
Inoculum	Activated sludge – city plant
Exposure Period	28 days
Auxiliary Solvent	
Analytical Monitoring	BOD by Closed system oxygen consumption measurement – soda lime. TOC/DOC
Remarks - Method	Reference substance – aniline Concentration of suspended solids – 30 mg/L Treatments: - water + test substance – 100 mg/L – vessel 1 - sludge + test substance – 100 mg/L – vessel 2, 3 and 4 - sludge + aniline – 100 mg/L – vessel 5 - control blank – activated sludge only – vessel 6 Temperature measured daily – 25°C BOD was measured by data sampler and autorecorder. At termination of study the dissolved organic carbon, test substance concentration and pH were measured.

RESULTS

Percentage biodegradation – ONLY in test solutions (Vessels 2, 3 & 4)

Method	% degradation			
	Vessel 2	Vessel 3	Vessel 4	Average
BOD	0	0	0	0
TOC	0	2	0	1

Remarks - Results	The reference substance (aniline) degraded by 75.3% after 28 d confirming the suitability of the inoculum and test conditions.. Solutions were not analysed for the test substance due to the rapid dissociation of the test material. Analysis for the dissociation products resulted in recoveries of between 94 and 101%.
CONCLUSION	Under the study conditions the test substance was not readily biodegradable.
TEST FACILITY	Kurume (2004)

8.1.2. Bioaccumulation

Not determined. The notified chemical rapidly dissociates in water and will not bioaccumulate.

8.2. Ecotoxicological investigations

8.2.1. Acute toxicity to fish

TEST SUBSTANCE: Notified chemcial

METHOD: OECD TG 203 Fish, Acute Toxicity Test -Static.
EC Directive 92/69/EEC C.1 Acute Toxicity for Fish –Static.

Species	Zebra fish (*Danio rerio*)
Exposure Period	96 h
Auxiliary Solvent	None
Water Hardness	2.1-2.5 mmol Ca^{2+} + Mg^{2+}/L
Analytical Monitoring	HPLC with UV detection
Remarks – Method	Based on range-finding tests it was determined that a limit test at 100 mg/L would be done. A measured amount of test substance was homogenized in water by ultrasonication and added to the test chamber without filtration and stirred for 24 h prior to the addition of fish. The concentration and stability of the test solution was determined at 0, 48 and 96 hours. The test solutions showed a light turbidity. Particulate matter was observed on the water surface and the bottom of the vessel. The test vessels, each with 10 fish, were covered, maintained between 21-22°C, exposed to a photoperiod of 16 dark/8 hours light and were aerated throughout the study. Temperature (21.1-21.8°C for test vessel and 21.3-21.6°C for control), pH (7.5-7.7 test vessel and 7.5-8.1 control) and dissolved oxygen (6.7-9.0 mg/L test solution and 6.9-10.3 mg/L control) were recorded daily. Observations were made at 3, 6, 24, 48, 72 and 96 hours with the fish being transferred to clean water for the observations.

RESULTS

Concentration mg/L		*Number of Fish*	*Mortality*				
Nominal	*Actual**		*1 h*	*24 h*	*48 h*	*72 h*	*96 h*
0	-	7	0	0	0	0	0
100	11.0	7	0	0	0	0	0

*Mean concentration the initial measured concentration 18.7 mg/L, 48 h measured concentration of 7.6 mg/L and 96 h concentration of 6.8 mg/L.

LC50	>100 mg/L at 96 hours. (nominal).
LOEC	100 mg/L at 96 hours. (nominal).
Remarks – Results	From the analytical method it is unclear whether the concentrations being measured were for the test substance or a dissociation product (noting that the solutions were stirred for 24 h prior to the addition of test organisms and that a stability test reported in the biodegradation study observed 100% dissociation of the notified chemical within 24 h). The fish showed changes in behaviour, swimming behaviour and respiration rate in all tested concentration groups at all times.

CONCLUSION: The notified chemical has an LC50 greater than its solubility at > 100 mg/L (nominal concentration). However, some sub-acute effects were observed.

TEST FACILITY: Hoechst Marion Roussell (1998g)

8.2.2.a Acute toxicity to aquatic invertebrates

TEST SUBSTANCE: Notified chemical

METHOD: OECD TG 202 Daphnia sp. Acute Immobilisation Test and Reproduction Test - Static.
EC Directive 92/69/EEC C.2 Acute Toxicity for Daphnia - Static.

Species	*Daphnia magna*
Exposure Period	48 hours
Auxiliary Solvent	None
Water Hardness	Not specified.
Analytical Monitoring	HPLC UV detection
Remarks - Method	Based on range-finding tests it was determined that a limit test at 100 mg/L would be done. A measured amount of test substance was homogenized in water by ultrasonication and added to the test chamber without filtration and stirred for 24 h prior to the addition of daphnia. The concentration and stability of the test solution was determined at 0 and 48 h. The test solutions showed a light turbidity. Particulate matter was observed on the water surface. The test vessels (2 replicates), each with 10 daphnia, were covered, maintained at 21^{o}C, exposed to a photoperiod of 16 dark/8 hours light and were not aerated throughout the study. Temperature (21.2-21.4°C for test vessel and 20.1-21.1°C for control) was recorded daily, while pH (7.3-7.6 for test vessel and 8.2-8.3 for control) and dissolved oxygen (8.4-8.6 mg/L for test vessel and 8.7-9.0 for control) were recorded at the start and end of the study. Observations were made at 24 and 48 hours. Two controls were done in parallel.

RESULTS

Concentration mg/L		*Number of D. magna*	*Number Immobilised*	
Nominal	*Actual*		*24 h*	*48 h*
0	-	20		
100	33.7*	20		

*Mean concentration the initial measured concentration 66.01 mg/L and 48 h measured concentration of 1.31 mg/L..

LC50	>100 mg/L at 48 hours (nominal).
NOEC	100 mg/L at 48 hours (nominal).
Remarks - Results	From the analytical method it is unclear whether the concentrations being measured were for the test substance or a dissociation product (noting that the solutions were stirred for 24 h prior to the addition of test organisms and that a stability test reported in the biodegradation observed 100% dissociation of the notified chemical within 24 h). No immobility was observed up to the limit of the solubility.

CONCLUSION The test material is not toxic to daphnia up to the limit of its solubility.

TEST FACILITY Hoechst Marion Roussell (1998h)

8.2.2.b Acute/chronic toxicity to aquatic invertebrates

TEST SUBSTANCE Notified chemical.

METHOD	OECD TG 202 Daphnia sp. Acute Immobilisation Test and Reproduction Test – semi static. EC Directive 92/69/EEC C.2 Acute Toxicity for Daphnia – Semi-static.
Species	*Daphnia magna*
Exposure Period	21 days
Auxiliary Solvent	None
Water Hardness	2.1-2.7 mmol Ca^{2+} + Mg^{2+}/L (test vessel) 2.1-2.5 mmol Ca^{2+} + Mg^{2+}/L (control vessel)
Analytical Monitoring	HPLC refractive index detection
Remarks - Method	Test concentrations were prepared by adding a weighed amount of test substance into a beaker, mixed with test medium and ultrasonicated for 10 min. Mixtures were then stirred for 24 h prior to adjusting the pH to

7.0-7.2 and passed through a 0.2 μm filter. Test media were refreshed every Monday, Wednesday and Friday during the study. All test solutions were observed to be clear. All environmental parameters (pH, Dissolved O_2 and temperature) were within acceptable ranges.

The EC50, NOEC and LOEC values were determined if possible, for the parameters mobility and reproductive output (as mean cumulative offspring) using he statistical software ToxRat Professional 2.09. The method of analysis is uncertain.

RESULTS

Concentration mg/L		Number of D. magna	*Number Immobilised*					
Nominal	*Actual*	10	*1 d*	*2 d*	*4 d*	*14 d*	*15 d*	*21 d*
0	-	10	0	0	0	0	0	0
1	1.014	10	0	0	0	0	0	0
3.2	3.250	10	0	0	0	0	0	0
10	10.049	10	0	0	0	0	0	0
32	31.907	10	0	0	0	2	7	8
100	98.410	10	0	5	10	10	10	10

LC50	22.3 (CI 16.3-30.6) mg/L at 21 days immobility (immobility of parent) 46.2 (CI 44.5-48.1) mg/L at 21 days reproduction
NOEC	10 mg/L at 21 days (immobility of parent) 10 mg/L at 21 days (reproduction)
LOEC	32 mg/L at 21 days (immobility of parent) 32 mg/L at 21 days (reproduction)
Remarks - Results	From the analytical method it is unclear whether the concentrations being measured were for the test substance or a dissociation product (noting that the solutions were stirred for 24 h prior to the addition of test organisms and that a stability test reported in the biodegradation observed 100% dissociation of the notified chemical within 24 h). The latter seems highly likely particularly as the analytical method used is not specific for the test material and would explain the apparently high water solubility in this study. In the control group, no mortality occurred and the mean number of living offspring produced per parent animal was 80.1, thus fulfilling the validity criteria for the test. All test animals in the highest test concentration died within 4 days of exposure. At 32 mg/L test level mortality 80% mortality was observed at the end of the study with mortalities first noted at 14 days. No mortalities occurred in the three lower test concentration. Surviving animals of all concentration groups showed no difference in the onset of brood production in comparison to the control and the reproduction rate in the three lowest test concentrations were not statistically different from the control.
CONCLUSION	The test material is very slightly toxic to daphnia under the study conditions (Mensink *et al.* 1995).
TEST FACILITY	Safety Science and Quality Services (2005)

8.2.3. Algal growth inhibition test

TEST SUBSTANCE	Notified substance
METHOD	EC Directive 92/69/EEC No. L383 C.3 Algal Inhibition Test.
Species	*Scenedesmus subspicatus*
Exposure Period	72 hours
Concentration Range	Nominal: 3.2, 5.8, 10, 18, 32, 58, 100, 180 mg/L

Measured* 2.2, 6.4, 11.1, 18.9, 29, 54, 88, 153 mg/L

*Measured as Al^{3+} through complexation with Alizarinred.

Auxiliary Solvent: None
Water Hardness: Not specified
Analytical Monitoring: Spectrophotometry
Remarks - Method: A 360 mg/L stock solution was prepared. Dispersion of the test material was achieved by ultrasonication for 45 min at 40°C and stirring. Test concentrations were prepared by dilution from the stock solution.

An initial cell density of 1×10^4 cells/mL was used. Constant illumination and stirring, and temperature maintained at between 22.1-236.78.1°C.
The addition of the test material to the test media resulted in a pH effect as shown below

Test Substance Concentration mg/L		pH	
Nominal	Actual	Initial	72 h
control		7.92	8.47
3.2	2.2	7.83	8.35
5.8	6.4	7.74	8.22
10	11.1	7.65	8.09
18	18.9	7.47	8.00
32	29	7.31	7.91
58	54	7.02	7.76
100	88	5.92	6.78
180	153	4.44	4.70
180 (pH control)	164	7.98	7.05

RESULTS

Biomass		*Growth*	
E_bC50 mg/L at 72 h	*NOE_bC mg/L*	*E_rC50 mg/L at 72 h*	*NOE_rC mg/L*
60 (54.7-65.2)	2.2	76 (68.5 – 83.6)	2.2

Remarks - Results: The solubility of the test substance in the test medium was checked. After 72 h the test substance had completely sedimented. In the pH control the pH was adjusted and no inhibition of growth was observed compared to the control.

CONCLUSION: Under the study conditions, the test substance is harmful to algae (United Nations 2003).

TEST FACILITY: Dr U Noack-Laboratorium (1998a)

8.2.4. Inhibition of microbial activity

TEST SUBSTANCE: Notified chemical

METHOD: OECD TG 209 Activated Sludge, Respiration Inhibition Test.
EC Directive 88/302/EEC C.11 Biodegradation: Activated Sludge Respiration Inhibition Test

Inoculum: Activated sewage sludge from a domestic STP
Exposure Period: 3 hours
Concentration Range: Nominal: 320, 580, 1000, 1800, 3200, 5800, 10000 mg/L
Remarks – Method: The study was conducted as a single test vessel per concentration and duplicate controls. Vessels were aerated during the tests, and O_2 consumption rates were monitored. Temperature was maintained at 21°C.

	Duplicate controls were run in parallel. Reference substance – Copper(II) sulphate pentahydrate Rate of respiration was determined after 3 hours contact. Total water hardness – 100 mg/L $CaCO_3$.
RESULTS	
EC50	1968 (CI 1629-2376) mg/L
NOEC	483 mg/L
Remarks – Results	Reference substance 3 h EC_{50} = 100 mg/L The validity criteria for control respiration rates variation and reference material toxicity were satisfied. Environmental parameters were within acceptable ranges.
CONCLUSION	Under the study conditions the test substance is not toxic to micro-organisms.
TEST FACILITY	Dr U Noack-Laboratorium (1998b)

9. RISK ASSESSMENT

9.1. Environment

9.1.1. Environment – exposure assessment

The proposed use and disposal pattern for the notified chemical suggests that direct release to the aquatic and terrestrial environmental compartments of the environment is unlikely and therefore no predicted environmental concentration (PEC) has been estimated for the notified chemical.

Wastes containing the notified chemical generated during pellet formulation and end-product moulding are expected to be disposed of to landfill or incinerated. Up to 165 kg per annum of the notified chemical could be disposed of to landfill, including as residues in empty containers. Most of this waste would be cured product in which case the chemical will be incorporated into an inert matrix and will be unavailable to the environment. It is unlikely that the notified chemical will leach into the water compartment due to its low solubility.

Should blooming of the notified chemical occur in the polymers that it has been incorporated in, the chemical will slowly make its way to the surface where it will not be volatile. In the event that these surfaces come into contact with water the chemical will dissolve, through dissociation, and be washed off the surface. This will occur in a very disperse manner.

At the end of their useful lives articles made containing the notified chemical would be disposed of to landfill or recycled.

The notified chemical rapidly dissociates in water and will not bioaccumulate.

9.1.2. Environment – effects assessment

The aquatic toxicity data submitted for the 4 taxa (fish, invertebrates, algae and micro-organisms) indicates that the chemical is slightly toxic to aquatic invertebrates and algae and slightly toxic to fish. The most sensitive species was algae with a reported NOEC of 2.2 mg/L at 72 hours. A predicted no effect concentration for aquatic organisms ($PNEC_{aquatic}$) of 44 µg/L has been derived by dividing this by a safety factor of 50 as chronic data is available.

9.1.3. Environment – risk characterisation

The notified chemical does not pose a significant risk to the environment based on its reported use pattern because there will be very low environmental exposure. The majority of the chemical will be contained in a cured polymeric matrix. The majority of the notified chemical will eventually be disposed of to landfill in the final products at the end of their useful lives.

Despite the low PNEC, it is appreciated that there is unlikely to be any release of the chemical into the aquatic environment under the proposed use patterns. Given the low aquatic exposure a meaningful PEC can not be calculated and levels are expected to be well below the safety margin.

Tests show that the notified chemical has a low potential to bioaccumulate and that it is not readily biodegradable. However, abiotic or slow biotic processes are expected to be largely responsible for the eventual degradation of the notified chemical.

9.2. Human health

9.2.1. Occupational health and safety – exposure assessment

The notified chemical is imported as a fine powder in 25 kg lined cardboard boxes. Transport or warehouse workers can be exposed in the event of accidental breach of the containers.

The main operation during which inhalation exposure could occur will be after slitting the inner polyethylene bag and scooping or suctioning the powder to the mixing vessel. This exposure is controlled by the use of LEV and dust masks if required. Some dermal or ocular exposure can

occur and will be controlled by the use of impervious gloves and safety goggles. Once the powder has been added to the mixing vessel, it is in a closed system and exposure should be precluded. In addition, the notified chemical is encapsulated within a matrix and should not be bioavailable. Therefore, exposure during subsequent moulding operations should also be precluded.

9.2.2. Public health – exposure assessment

Under normal circumstances the public should potentially only contact the notified chemical when it is incorporated in a solid matrix. However, the electrical components and furniture components are not likely to be contacted by the public and public exposure would therefore be restricted to release of the chemical after a transport accident.

9.2.3. Human health – effects assessment

The notified chemical was of low acute oral and dermal toxicity in rats, was not a skin irritant and was a slight eye irritant in rabbits and was not a skin sensitiser in guinea pigs. No systemic toxicity was identified in a 28-day repeated oral toxicity study and the notified chemical was neither mutagenic in bacteria nor clastogenic in Chinese Hamster V79 cells in vitro.

Based on the available data, the notified chemical is not classified as a hazardous substance in accordance with the NOHSC *Approved Criteria for Classifying Hazardous Substances* (NOHSC 2004).

9.2.4. Occupational health and safety – risk characterisation

Given the limited opportunity for exposure (limited to transfers of the imported notified chemical in powder form to the mixing vessel in which the plastic is formed) and the low hazard indicated by a complete data set for this standard notification, there is virtually no risk of adverse health effects to workers involved in plastic manufacture and moulding operations. There is a low probability that nuisance dust levels could exceed the NOHSC exposure standard of 10 mg/m^3 (NOHSC, 1995) and this would be unlikely to occur. The main risk to workers will be contact with hot plastic and this can be expected on an intermittent basis.

9.2.5. Public health – risk characterisation

As the notified chemical is of low hazard and exposure of the public is unlikely, the risk to the public from importation of the notified chemical and use and disposal in the manner described is considered to be negligible.

10. CONCLUSIONS – ASSESSMENT LEVEL OF CONCERN FOR THE ENVIRONMENT AND HUMANS

10.1. Hazard classification

Based on the available data the notified chemical is not classified as hazardous under the NOHSC *Approved Criteria for Classifying Hazardous Substances*.

10.2. Environmental risk assessment

The chemical is not considered to pose a risk to the environment based on its reported use pattern.

10.3. Human health risk assessment

10.3.1. Occupational health and safety

There is Low Concern to occupational health and safety under the conditions of the occupational settings described.

10.3.2. Public health

There is Negligible Concern to public health when used as described.

11. MATERIAL SAFETY DATA SHEET

11.1. Material Safety Data Sheet

The MSDS of the product to be imported containing the notified chemical provided by the notifier was in accordance with the NOHSC *National Code of Practice for the Preparation of Material Safety Data Sheets* (NOHSC 2003). It is published here as a matter of public record. The accuracy of the information on the MSDS remains the responsibility of the applicant.

11.2. Label

The label for the product to be imported containing the notified chemical provided by the notifier was in accordance with the NOHSC *National Code of Practice for the Labelling of Workplace Substances* (NOHSC 1994). The accuracy of the information on the label remains the responsibility of the applicant.

12. RECOMMENDATIONS

CONTROL MEASURES
Occupational Health and Safety

- A copy of the MSDS should be easily accessible to employees.
- If products and mixtures containing the notified chemical are classified as hazardous to health in accordance with the NOHSC *Approved Criteria for Classifying Hazardous Substances*, workplace practices and control procedures consistent with provisions of State and Territory hazardous substances legislation must be in operation.

Environment

- The following control measures should be implemented by plastic manufactures to minimise environmental exposure during use of the notified chemical:
  - Ensure all process areas are bunded with all drains going to collection pits or on-site treatment plants.

Disposal

- The notified chemical should be disposed of by recycling, landfill or incineration

Emergency procedures

- Spills/release of the notified chemical should be handled by containment, collection and storeage in a sealable labelled container ready for disposal.

12.1. Secondary notification

The Director of Chemicals Notification and Assessment must be notified in writing within 28 days by the notifier, other importer or manufacturer:

(1) Under Section 64(2) of the Act:
  - if any of the circumstances listed in the subsection arise.

The Director will then decide whether secondary notification is required.

No additional secondary notification conditions are stipulated.

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Albemarle

Comment: Comments on the DRAFT of July 2012 Design for Environment Screening Level Hazard Assessment of Decabromodiphenyl Ether (DecaBDE); CASRN 1163-19-5

The materials referenced in the "List of Appendixes" are available upon request by contacting Emma Lavoie at lavoie.emma@epa.gov or 202-564-0951.

COMMENTS
on the
DRAFT of July 2012
Design for the Environment Screening Level Hazard Assessment of Decabromodiphenyl Ether (DecaBDE); CASRN 1163-19-5

A screening level hazard assessment, by its nature, is superficial. DecaBDE is a data-rich chemical, with conflicting information on certain endpoints. Resolution of these apparent differences requires in-depth analysis; however, the nature of a screening assessment does not allow for such analysis. As a result, DecaBDE's actual hazard has been misunderstood. These comments attempt to clarify DecaBDE's database and additionally provide new information on carcinogenicity, metabolism, bioaccumulation, and chemical analysis.

Page 4-8. Identifying and Reviewing Measured Data. DfE states that the hazard assessment "resulted in a comprehensive search of the literature for available experimental data" and that for well-characterized chemicals "this usually resulted in the collection of recent high-quality reviews or peer-reviewed risk assessments".

DecaBDE is a well-characterized chemical having experimental data developed over the more than 30 years of its commercial use. A recent high quality review of DecaBDE's toxicology[1] that included a human health risk assessment and published in a highly regarded journal, Critical Reviews in Toxicology, was not cited. This is a serious deficiency in DfE's draft document, and suggests that DfE's hazard assessment did not "lead to a thorough understanding of behavior and effects of the chemical" (pg 4-8, 4.2. Data Sources and Assessment Methodology). Importantly, the oral reference dose derived in Hardy et al. (2009), 4 mg/kg/d, is not indicative of health hazards.

Other recent, high quality data[2],[3] was only included in DfE's draft assessment after an initial review of the hazard summary allowed to manufacturers in the spring of 2012. This initial review suggested that DfE's assessment of DecaBDE was largely based on IRIS 2008[4] (developmental and neurotoxicity) and EPA 2008[5] (carcinogenesis).

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[1] Hardy et al. 2009. Toxicology and Human Health Risk Assessment of Decabromodiphenyl Ether. Critical Reviews in Toxicology 39(S3):1-44.
[2] Biesemeier et al. 2010. Effects of dose, administration route, and/or vehicle on decabromodiphenyl ether concentrations in plasma of maternal, fetal, and neonatal rats and in milk of maternal rats. Drug Metab Dispo 38(10):1648-1654.
[3] Biesemeier et al. 2011. An oral developmental neurotoxicity study of decabromodiphenyl ether (DecaBDE) in rats. Birth Defects Res Part B 92:17-35.
[4] IRIS 2008. 22334455-Decabromodiphenyl ether (BDE-209) (CASRN 1163-19-5). http://www.epa.gov/iris/subst/0035.htm
[5] EPA 2008. Toxicological Review of Decabromodiphenyl ether (BDE-209) (CAS No. 1163-19-5). In Support of Summary Information on the Integrated Risk Information System (IRIS) . EPA/635/R-07/008F.

IRIS 2008 and EPA 2008 were performed before results of a guideline/GLP-compliant developmental neurotoxicity (DNT) study on DecaBDE were available. IRIS 2008 based its findings on a non-guideline, non-GLP study[6] whose experimental design has been found unacceptable by authors affiliated with EPA[7]. The guideline/GLP-compliant DNT study resulted in a NOAEL of 1000 mg/kg/d, but IRIS's assessment has not been updated. DfE's assessment of DecaBDE's potential for developmental effects and neurotoxicity aligns with that of IRIS 2008 (pages 4-282 and 4-287). DecaBDE's potential for developmental effects and neurotoxicity is properly based on the most reliable information available. This is reflected in guideline/GLP-compliant studies published in the peer-reviewed literature on prenatal developmental effects (Hardy et al. 200x[8], Biesemeier et al.2010) and developmental neurotoxicity (Biesemeier et al. 2011). These studies produced NOEL/NOAELs of 1000 mg/kg/d.

In evaluating the cancer endpoint, EPA 2008 did not consider an early 2-year dietary study in rats[9] that found no evidence of carcinogenicity or toxicity. The negative results in the 1975 study indicate the limited evidence of cancer at substantially higher doses[10], on which DfE based its hazard rating, is dose-related.

Page 4-269. Synonyms. Albemarle Corporation is a manufacturer of DecaBDE, and is familiar with names associated with this substance. The following are not known synonyms for this substance: AFR 1021, BR 55N, Bromkal 83-10DE; Claiban F/R-P; DB 10 through 102; DP 10F; EB 10 through 10WS; EBR 700, F/R-P 53; Fire Cut 83D; Flame Cut 110R and Br 100; FR10; FR-PE and PE(H); FRP53; Nonnen DP 10 and DP 10(F); PBED 209; Planelon DB through DB101; Plasafety EB 10 and EBR 700. These names may be found on the Internet as associated with DecaBDE; however, the sources' validity has not been verified. Further, a CAS number other than 1163-19-5 is often linked to these so-called synonyms. Repetition of unverified information does not advance our understanding.

Page 4-269. Chemical Considerations. DfE indicates measured values from experimental studies were incorporated into the estimations performed by EPI v4.0. This problematic for substances such as DecaBDE that have limited solubility in water *and* organic solvents and are difficult to analyze. Depending on the study, the measured values may be the best available, but given the problems inherent in analysis, may not be accurate enough to be included in an estimation program. Further, DecaBDE's measured

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[6] Viberg et al. 2003. Neurobehavioral derangements in adult mice receiving decabrominated diphenyl ether (PBDE 2009) during a defined period of neonatal brain development. Toxicol Sci 76:112-120.

[7] Holson et al. 2008. Statistical issues and techniques appropriate for developmental neurotoxicity testing. A report from the ILSI Research Foundation/Risk Science Institute expert working group on neurodevelopmental endpoints. Neurotoxicology and Teratology 30:326-348.

[8] Hardy et al. 2002. Prenatal oral (gavage) developmental toxicity study of decabromodiphenyl oxide in rats. Int J Toxicol 21:83-91.

[9] Kociba et al. 1975. Results of a two-year dietary feeding study with decabromodiphenyl oxide (DBDPO) in rats. Journal of Combustion Toxicology 2:268-285. APPENDIX 1.

[10] NTP 1986. Toxicology and Carcinogenesis Studies of Decabromodiphenyl Oxide (CAS No. 1163-19-5) in F344/N Rats and B6C3F1 Mice (Feed Studies). Research Triangle Park, NC. National Toxicology Program Technical Report Series No. 309.

melting point reflects that of the commercial product, and not that of 'pure BDE 209' congener. Estimations are run on the molecule ('pure BDE 209 congener), and melting points should only be entered if run on pure substances.

Albemarle Corporation has considerable experience running the EPI software on brominated flame retardants. Our experience indicates the most predictive results are based on estimations performed using the structure only. Entry of measured values into the software produces unreliable results.

Page 4-270. Metabolites, Degradants and Transformation Products. DfE states DecaBDE's metabolites, degradants and transformation products are lower brominated diphenyl ethers, a range of penta- to nonaBDEs (with 224456-hexaBDE being most prevalent, and polybrominated dibenzofurans. European Chemicals Bureau 2002 (ECB 2002)[11] is given as the reference.

ECB 2002 did not reach this conclusion.

ECB 2002, pp 17-18, on transformation/breakdown products, and pp 130-131 on metabolism are reproduced below.

With respect to transformation/breakdown products, ECB 2002 (page 17-18) concluded:

[11] ECB 2002. European Chemicals Bureau. EU Risk Assessment Report for Bis(Pentabromophenyl) Ether. CAS No. 1163-19-5. EINECS No. 214-604-9. pp 1-294.

2.4 BREAKDOWN/TRANSFORMATION PRODUCTS

There is a large body of literature that shows that, under certain combustion/pyrolysis conditions, decabromodiphenyl ether, and polybrominated diphenyl ethers in general, can form brominated dibenzofurans and brominated dibenzo-*p*-dioxins. This is discussed in detail for all the commercial polybrominated diphenyl ethers in Appendix A. Generally, the amounts of brominated dibenzofurans and dibenzo-*p*-dioxins formed from decabromodiphenyl ether appear to be less than from other brominated diphenyl ether compounds tested. Factors that appear to affect the formation include the temperature, residence time at the temperature, the presence of oxygen, the type of polymer matrix and the presence of other additives (e.g. antimony trioxide). Virtually complete destruction of decabromodiphenyl ether and any possible breakdown products appears to occur at temperatures of 800°C and above for 2 seconds.

Of possible environmental concern is the release of brominated dibenzofurans (and to a lesser extent brominated dibenzo-*p*-dioxins) from incineration of plastics containing decabromodiphenyl ether and during accidental fires involving articles containing decabromodiphenyl ether.

In the case of accidental fires, given the large amounts of toxic products known to be formed, notably chlorinated dibenzo-*p*-dioxins and dibenzofurans, but also non-halogenated products such as polycyclic aromatic compounds, the presence of decabromodiphenyl ether is unlikely to significantly affect the total release of toxic products from fires as, in most cases, decabromodiphenyl ether will only constitute a small proportion of the total halogenated material present in a fire.

Regulations on the design of municipal incinerators require a minimum incineration temperature of 850°C for 2 seconds (EEC, 1989a and 1989b). Draft proposals for hazardous waste incinerators require a minimum temperature of 1,000°C. From the information reported in Appendix A, it can be seen that a combustion temperature of 850°C is adequate to prevent the formation of brominated dibenzofurans and dibenzo-*p*-dioxins during incineration/pyrolysis of decabromodiphenyl ether in the laboratory.

In the United Kingdom, incineration processes are covered under the Environmental Protection Act (1990). Under Part 1 of the Act, two separate pollution control regimes were established under which specified industrial processes must apply for authorisation to operate: Integrated Pollution Control (IPC), regulated by the Environment Agency (formerly HMIP), and Local Authority Air Pollution Control (LAAPC), regulated by the local authorities. Under LAAPC, existing general waste incineration processes under 1 tonne/hour should be subjected to an emission standard for chlorinated dioxins of 1.0 ng TEQ/m^3 by June 2000. Until then, such incinerators should have secondary combustion zone temperatures and residence times of 850°C and 2 seconds. New general waste incinerators should meet the 1.0 ng TEQ/m^3 limit from September 1995. Under IPC, municipal solid waste (MSW) incinerators and other specified scheduled processes will have to conform to an emission standard for chlorinated dioxins of 1.0 ng TEQ/m^3, with a guide value of 0.1 ng TEQ/m^3. All new plants will have to conform to this standard, with existing plants required to meet this standard over various time scales, extending to the year 2000. It is estimated that chlorinated dioxin emissions from these processes should be reduced by 90%.

Given the similarities between chlorinated and brominated dioxins and furans, incinerator design and abatement technologies employed for chlorinated dioxins and furans should also be effective in limiting the risk from the brominated analogues.

Other disposal/recycling practices for articles containing decabromodiphenyl ether may have the potential to release polybrominated dibenzofurans and dibenzo-*p*-dioxins to the environment, and these are considered further for polybrominated diphenyl ethers as a group in Appendix A.

A discussion of the breakdown/transformation products formed during production of decabromodiphenyl ether and processing of polymers containing decabromodiphenyl ether is given in Appendix D.

With respect to metabolism, ECB 2002 (page 130-131) concluded:

> **4.1.2.1.3 Summary of toxicokinetics, metabolism and distribution**
>
> Only limited data on human toxicokinetic are available. Those data indicate that DBDPO can be absorbed into the body and are distributed to the blood and the adipose tissue. Few data on human hair samples reveal the presence of DBDPO but the route of exposure is unknown. Some results show that DBDPO and others PBDPOs congeners are bioavailable and that in some occupational conditions, slightly increased plasma levels of DBDPO are observed. There are no data available on the rate of elimination or of bioaccumulation of DBDPO in human adipose tissue neither for PeBDPO or OBDPO but given the low rate of oral absorption in rats, a low bioaccumulation potential might be anticipated. Following pregnancy HxBDPO and others PBDPOs such as TeBDPO and PeBDPOs are excreted in the breast milk. Based, on the low rate of oral absorption in rats and the low bioaccumulation potential of DBDPO, the rapporteur might anticipate a rather low excretion of this compound in the breast milk. A recent survey of the levels of DBDPO in human milk was conducted by Ryan and Patry (2001) in Canada. The analysis of decabromodiphenyl ether in these samples was reported to be difficult. However, little or no decabromodiphenyl ether could be detected in human milk samples. Therefore a rather low excretion of this compound in the breast milk might be anticipated. Animal data indicate that in rats there is a low absorption of DBDPO through the gastro-intestinal tract (approximately 6-9.5%) and that the principal route of elimination is via the faeces. Some DBDPO is absorbed intact from the intestine and excreted intact or in the form of metabolites (e.g. debrominated hydroxylated diphenyl oxides). DBDPO following intravenous administration is subject to hepatic metabolism with production of three main metabolites. However, a gastrointestinal metabolisation may also be assumed. Only trace amount of bromine compounds was found in tissues and in brain of neonatal mice exposed on postnatal day 3, 10 or 19. However the toxicological significance of this last finding is unclear. Accumulation is only observed in liver at a low level and in adipose tissue. DBDPO is not an inducer of xenobiotic metabolism including UDPG-transferase. However, the absence of inducer effect observed at a relatively low concentration of DBDPO does not preclude a lack of an inducer effect at higher concentrations. There are no data on dermal absorption neither on DBDPO nor on PeBDPO or OBDPO. However based on DBDPO physicochemical properties and analogy with PCBs, a maximal dermal absorption of 1% may be assumed.
>
> Experimental data do not allow to assess pulmonary absorption. Pulmonary exposure may occur due to the small particle size (<5 µm), however, systemic absorption via the pulmonary route is unknown.

DfE's conclusion with respect to 2,2',4',4',5,6-hexaBDE appears to be derived from Noyes et al. 2011[12], e.g. a 28-d dietary study in fish. As discussed later in these comments, DecaBDE was not bioaccumulated in fish based on the measured amounts of DecaBDE or DecaBDE-plus-presumed-metabolites. The total amount of presumed

[12] Noyes et al. (2011). Accumulation and debromination of decabromodiphenyl ether (BDE-209) in juvenile fathead minnows (Pimephales promelas) induces thyroid disruption and liver alterations. Tox Sci 122(2):265-274.

metabolites was <3% of the cumulative DecaBDE dose. While Noyes et al. did report the hexaBDE congener was present in the highest amount of the lower brominated diphenyl ethers detected, the amount was insignificant (~1.3% of DecaBDE's cumulative dose) and does not merit inclusion in this section's summary.

Other experimental evidence also indicates the metabolic conversion of DecaBDE to lower brominated diphenyl ethers is minimal in fish. Key studies in fish are Kierkegaard et al. 1999[13], Stapleton et al. 2004[14], Stapleton et al. 2006[15], and Tomy et al. 2004[16]. These studies are summarized:

- Kierkegaard et al. 1999: Approximately 0.005% uptake of DecaBDE from diet by fish over 120 d of feeding. No evidence of debromination to BDE47, 99 or 100, which are the major PBDEs detected in wild-caught fish.

- Stapleton et al. 2004: No measurable uptake of BDE209 from diet by fish over 90 d. Presumed metabolites ~ 0.4% of dose.

- Stapleton et al. 2006: Approximately 0.39% uptake of BDE209 by fish from diet after feeding for 120 d. Uptake as a percent of dose similar to that reported in rats by NTP 1986. No evidence of in vitro metabolism by microsomes at 1 hr, production of lower brominated diphenyl ethers after 24 h incubation.

- Tomy et al. (2004): BDE209's 'assimilation efficiency' and biomagnification factor (BMF) ~0.3 after 56 d. 'Strongest' evidence for debromination said to be 3 congeners making up 4-5% total PBDEs detected in fish.

The above 4 papers are typically cited as evidence of DecaBDE's debromination in fish show no to ~0.4% uptake of BDE209 from food in studies ranging from 56 to 120 days. None of the papers provided detailed compositional information on the test article, *e.g.* lower brominated diphenyl ether content. Thus, any lower brominated diphenyl ethers detected in fish may have been derived from the test article. One of the papers (Tomy *et al.*) based their debromination conclusions on slower *than expected* depuration rates and longer *than expected* half-lives after repeated administration of 13 PBDE congeners. This paper used fiberglass aquaria, which is totally inappropriate for studies of PBDEs, and did not report whether food/feces were regularly siphoned from the tanks. The other papers also did not report siphoning. These deficiencies do not allow a conclusion that BDE209 is 'debrominated' by fish. Further, biotransformation would occur only on that portion of the dose absorbed by the fish. The minimal uptake reported in all four studies indicates that metabolism of BDE209 would be negligible. The one study, Le Beuf *et al.*

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[13] Kierkegaard *et al.* 1999. Dietary uptake and biological effects of decabromodiphenyl ether in rainbow trout (Oncorhynchus mykiss). *Environ. Sci. Technol.* 33, 1612-17.

[14] Stapleton *et al.* 2004. Debromination of the flame retardant decabromodiphenyl ether by juvenile carp (Cyprinus carpio) following dietary exposure. Environ. Sci. Technol. *38,* 112-119.

[15] Stapleton et al. 2006. In vivo and in vitro debromination of decabromodiphenyl ether (BDE 209) by juvenile rainbow trout and common carp. Environ Sci Technol. 40(15):4653-8.

[16] Tomy et al. 2004. Bioaccumulation, biotransformation, and biochemical effects of brominated diphenyl ethers in juvenile lake trout (Salvelinus namaycush). Environ Sci Technol. 38(5):1496-504.

2006[17], reporting detailed composition of the test article found no evidence for BDE209's bioconversion to lower brominated diphenyl ethers.

Crimmins et al. (2012)[18] report a 1980-2009 temporal trend record of PBDEs (BDE 47, 99, 100, 153, 154) in Great Lakes' top predator fish shows declining levels in trout. While a similar declining trend was not observed in walleye (the other top predator fish assessed), concentrations began leveling off in the late 1990s with no obvious trend since then. If DecaBDE degradation were making a substantial contribution to these lower brominated diphenyl ethers, declining levels would not be expected given DecaBDE's continued use and the cessation of the penta- and octaBDE product.

A similarly low metabolism to lower brominated diphenyl ethers has been reported in rats. Please see the discussion under ADME and Bioaccumulation, and the studies of Huwe et al.

New information relates to DecaBDE's on-column debromination. Reports indicating DecaBDE's biotransformation to lower brominated congeners[19],[20],[21],[22],[23],[24],[25] typically used gas chromatography/mass spectrometry (GC/MS). These studies frequently had poor recoveries of the BDE 209 congener, attributable to DecaBDE's low solubility in most common organic solvents and its high adsorption to any kind of matrix, organic and inorganic, and to glassware. Incomplete recovery can lead to a conclusion that the parent compound has been metabolized (see Huwe et al. 2008[26], page 2699). GC/MS analyses require very high temperatures to vaporize DecaBDE in the injection port (melting point ~305°C0 and to elute DecaBDE through the GC column (up to 350°C). Unvaporized DecaBDE will adhere to the injection port, causing sample carry-over and serving as a source of degradants. The high elution temperature required and DecaBDE's long on-column retention due to its high adsorptive properties can also result in degradation – thermogravimetric analysis demonstrates DecaBDE undergoes approximately 1% weight loss at 290°C. DecaBDE's potential for injection port or on-column degradation has not

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[17] Le Beuf *et al.* 2006. Effects of deBDE and PCB-126 on hepatic concentrations of PBDEs and methoxy-PBDEs in Atlantic tomcod. Environ Sci Technol. 40(10):3211-6.

[18] Crimmins et al. 2012. Polybrominated diphenyl ethers (PBDEs): Turning the corner in Great Lakes trout 1980-2009. Environ Sci Technol 46:9890-9897.

[19] Gerecke et al. 2006. Anaerobic degradation of decabromodiphenyl ether. Environmental Sci Technol 39:1078-83.

[20] Takers et al. 2008. Reductive debromination of polybromination diphenyl ethers in anaerobic sediment and a biomimetic system. Environ Sci Tech 42:1157-64.

[21] La Guardia et al. 2007. Evidence of debromination of decabromodiphenyl ether (BDE209) in biota from a wastewater receiving stream. Environ Sci Tech 41:6663-70.

[22] He et al. 2006. Microbial reductive debromination of polybrominated diphenyl ethers (PBDEs). Environ Sci Tech 40:4429-34.

[23] Kierkegaard et al. 1999 Environ Sci Technol 33:1612-1617.

[24] Stapleton et al. 2004 Envrion Sci Technol 38:112-119.

[25] Tomy et al. 2004. Bioaccumulation, biotransformation, and biochemical effects of brominated diphenyl ethers in juvenile lake trout (Salvelinus namaycush). Environ Sci Technol 38:1496-1504. Environ Sci Technol 38:1496-1504.

[26] Huwe et al. 2008. Comparative absorption and bioaccumulation of polybrominated diphenyl ethers following ingestion via dust and oil in male rats. Environ Sci Technol 42:2694-2700.

been taken into account in the published literature with respect to debromination, and has caused misinterpretation of the study results.

DecaBDE's adsorption on the injection port and column can be handled with 1, preferably 2, toluene purges between samples, frequently cleaning of the injection port, and avoidance of glass wool. Unless these steps are taken, DecaBDE can be expected to degrade with a resultant faulty interpretation due to detection of lower brominated diphenyl ethers. None of the studies reporting DecaBDE's biotransformation to lower brominated diphenyl ethers reported these procedures in their analytical methodology.

This section would more correctly reflect the available information by indicating DecaBDE is eliminated in the feces as the parent molecule, largely without prior systemic circulation, and that minimal metabolism may occur (For example, Huwe et al. 2007[27] estimated 1% of a total BDE 209 dose appeared metabolized to 1 nonaBDE and 2 octaBDEs). Brominated dibenzofurans may form under certain combustion or pyrolysis conditions.

Page 4-271. Vapor Pressure. A copy of this guideline-GLP compliant study[28] will be forwarded separately to DfE so that the reference can be updated.

Page 4-271. Water Solubility. A copy of this guideline-GLP compliant study[29] will be forwarded separately to DfE so that the reference can be updated.

Page 4-271. Log Kow. A copy of this guideline-GLP compliant study[30] will be forwarded separately to DfE so that the reference can be updated.

Page 4-272. Toxicokinetics. We agree that the data indicate DecaBDE is poorly absorbed following oral and dermal exposure. DfE's following comment that "even low levels of decabromodiphenyl ether are physiologically relevant due to its chemical properties" is not valid. DecaBDE is not reactive and is essentially inert. It is very poorly soluble in water and most organic solvents. DecaBDE has NOAELs of >= 1000 mg/kg/d in repeated dose studies (NTP 1986 14-d and 90-d studies, Hardy et al. 2002, Biesemeier et al. 2010, Biesemeier et al. 2011) and is not bioaccumulative (EPA 2008). These properties indicate low levels are *not* physiologically relevant. This comment should be deleted.

We agree with that DecaBDE is primarily eliminated in the feces as the parent molecule.

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[27] Huwe et al. 2007. Accumulation, whole-body depletion, and debromination of decabromodiphenyl ether in male Sprague-Dawley rats following dietary exposure. Environ Sci Technol 41:2371-2377; Additions and Corrections 41:4486.

[28] Stenzel and Nixon. 1997. Decabromodiphenyl oxide (DBDPO): Determination of the vapor pressure using a spinning rotor gauge. Wildlife International, Ltd. Easton, MD. APPENDIX 2.

[29] Stenzel and Markley. 1997. Decabromodiphenyl oxide (DBDPO): Determination of the water solubility. Wildlife International, Ltd. Easton, MD. APPENDIX 3.

[30] MacGregor and Nixon. 1997. Decabromodiphenyl oxide: Determination of n-octanol/water partition coefficient. Wildlife International, Ltd. Easton, MD. APPENDIX 4.

The statement re monitoring studies in human volunteers should be clarified. To the best of our knowledge, no studies have been conducted whereby human volunteers ingested a known dose of DecaBDE with subsequent monitoring of blood and breast milk. The studies referred to in the draft DfE document were publications where samples collected from volunteers without known exposures were analyzed for DecaBDE. This is an important distinction because rigorous attempt at analysis of DecaBDE in human serum and breast milk have been unsuccessful.[31], [32]

Before DfE definitively states that DecaBDE has been detected in human breast milk, a careful scrutiny of the analytical methods in the cited reports should be performed. As late as 2010, the US Centers for Disease Control (CDC) has been unable to measure DecaBDE in breast milk (Daniels et al. 2008, page 158, 2nd column):

> We assessed variability by individual characteristics only among the congeners detected in > 70% of the participants. We were unable to measure BDE-209, the primary congener of the decaBDE formulation, which is the only brominated flame retardant still produced in the United States. BDE-209 is stable but less likely to bioaccumulate and be detected at remarkable levels in human tissue compared with the lower brominated congeners because of its short half-life (i.e., 2 weeks in humans) (Sjodin et al. 2003; Thuresson et al. 2006). According to the Agency for Toxic Substances and Disease Registry (2004), "the lower brominated PBDEs are much more likely than decaBDE to be stored in the mother's body and released during pregnancy, cross the placenta, and enter fetal tissues. Because lower brominated PBDEs dissolve readily in fat, they can accumulate in breast milk fat and be transferred to babies and young children."

The inability of CDC to analyze DecaBDE in breast milk (or serum) is significant given that A. Sjodin, now with the CDC, was the first to report detection of DecaBDE in human blood when he was a graduate student in Sweden. If A. Sjodin using a specially designed and constructed laboratory at the CDC cannot analyze DecaBDE in human blood or milk,

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[31] Sjodin et al. 2008. Serum Concentrations of Polybrominated Diphenyl Ethers (PBDEs) and Polybrominated Biphenyl (PBB) in the United States Population: 2003–2004. Environ Sci Technol 42(4): 1377-1384.

[32] Daniels et al. 2010. Individual characteristics associated with PBDE levels in U.S. human milk samples. Environ Health Perspectives 118(1):155-160.

then reports of DecaBDE's detection in similar matrixes by other researchers should be viewed with great skepticism.

CDC's estimated serum levels of 2 ng/g lw for the U.S. general population (Sjodin et al. 2008) should be included. DfE should take into consideration that concentrations in milk would be derived from serum. At serum concentrations of 2 ng/g lw, movement into breast milk is expected to be negligible given DecaBDE's diffusion limited passage through cell membranes.

DfE should rely on the most relevant and reliable data, e.g. that of CDC. We recommend deleting the comment regarding human monitoring studies.

Page 4-272. Dermal Absorption in vitro. Please indicate that *skin* of hairless mice was used in this in vitro study. The primary reference is Hughes et al. 2001. Food and Chemical Toxicology 39:1263-1270.

Page 4-273. Adding "Oral ADME in vivo" in the Property/Endpoint column is suggested.

The two studies reported on this page were part of the work performed by the US National Toxicology Program and are included in the 1986 NTP TR 309. APPENDIX 4 of these comments contains the section of TR 309 (Appendix O) reporting these studies.

The first study is described in the DfE document as follows:

> F344/N male rats fed 238 to 51,000 ppm unlabeled DBDPO (97.9-99.2% pure) in the diet on days 1-7 and ^{14}C DBDPO on day 8. Average daily consumption estimated to be 3,718 mg/kg-day.
>
> 91.3% of radioactivity was recovered in the feces 72 hours after exposure. Recovery was not related to administered dose. Low level of radioactivity in the liver and fat (0.064% and 0.008% of dose in liver for low and high dose, respectively; 0.157 and 0.09% in fat for low and high dose, respectively)

We suggest the following revision to provide corrections and important details:

> "Uptake and Disposition of ^{14}C-DecaBDE after Dietary Exposure. F344/N male rats fed 238 to 51,000 ppm unlabeled DecaBDE in the diet on days 1-7 and equal doses of ^{14}C-DecaBDE on day 8. Analysis of Day 9-12 urine and feces. Analysis of Day 12 liver and fat.

Within 72 hours post-dosing, 91 to 101% of the radiolabel was recovered in the feces. Recovery was not related to the unlabelled dose. Low levels of radioactivity were detected in liver and fat. Liver: mean of 0.02% of the ^{14}C-dose in the 6 groups, range 0.006 – 0.064%. Fat: mean of 0.11% of the ^{14}C-dose, range of 0.072 – 0.161%.

The second study is described as follows:

F344/N male rats fed 277 or 48,000 ppm unlabeled DBDPO on days 1-7 and 9-10 or 9-11 and ^{14}C DBDPO on day 8. Doses were equivalent to 22-25 and 4500-5000 mg/kg-day.

82.5% of radioactivity was recovered in feces. Recovery was not related to administered dose. Excretion in the urine was ≤ 0.01%. Trace levels of radioactivity were found in all major organs and tissues with the highest concentration found in the liver, kidney, lung, skin and adipose tissue.

DBDPO and 3 main metabolites were detected in the feces. % of metabolites increased with increasing DBDPO concentration in diet, but DBDPO was primary compound eliminated.

We suggest the following revision to provide further important details:

"Uptake and Disposition of ^{14}C-DecaBDE at 24, 48 and 72 hours after Exposure. F344/N male rats fed diets containing 0.0277% or 4.80% DecaBDE on days 1-7, equal amounts of ^{14}C-DecaBDE on day 8, and sacrificed 24, 48 or 72 hours post-dosing with the radiolabel. Blood, urine, feces, liver, kidney, lung, muscle, fat, skin, brain, gut contents and gut tissue were analyzed.

Recovery of radioactivity in the feces ranged from 82.5% to 86.4% and was not related to the dietary dose of unlabelled DecaBDE or the time of sacrifice. The % of dose remaining in the gut contents (<4%) and gut tissue (<0.04%) decreased with time after sacrifice.

Radioactivity in the liver declined with time post-dosing, e.g. 0.449% of the dose at 24 h, 0.213% at 48 hr, and 0.016% to 0.109% at 72 hours. The maximum % of dose in other tissues was as follows: kidney, 0.016%; spleen, 0.003%; lungs,

0.011%, brain, <0.001%), muscle (considered 50% of body weight), 0.0248%; fat (considered 7% of body weight), 0.077%; and skin (considered 16% of body weight), 0.0252%.

Extracts of liver demonstrated the radioactivity was associated with the parent DecaBDE molecule.

HPLC analysis of day 9-11 pooled fecal extracts contained the parent DecaBDE molecule and 3 additional radiolabeled peaks, totaling 1.5% of the recovered radioactivity in the low dose. The 3 peaks had shorter retention times than the parent molecule. Three impurities were present in the characterized unlabelled test article; 3 nonaBDEs are typical impurities in DecaBDE products. The two main impurities were identified as nonabromodiphenyl ethers. The third impurity was not identified due to its low level. The radiolabeled test article was 97.9% to 99.2% pure and contained 2.1% to 0.8% impurities. The impurities were not identified, but had retention times shorter than DecaBDE and are likely the typical nonaBDEs. These peaks were referred to as "metabolites" in the NTP report, but more likely represent the impurities in the test article."

Page 4-274. Adding "Disposition After IV Dosing" in the Property/Endpoint column is suggested.

The first study is described as:

Intravenous study in F344/N rats injected with 1.07 mg/kg ^{14}C DBDPO 75% of intra-venous dose was detected in feces and gut contents after 72 hours (suggests biliary excretion). Remaining ^{14}C DBDPO was detected in tissues, mainly in muscle, skin, liver and fat. Trace amounts of radioactivity were detected in urine, the spleen and brain. Excreted material in the feces was primarily unchanged DBDPO.

And qualified with

Study details reported in a secondary source; 9.5% of the administered dose was found in the tail indicating that the dose was delivered incompletely and an unknown amount was given through the tail vein.

We suggest the following revision to provide important details:

> "Disposition of ^{14}C-DecaBDE after IV Dosing. At 72 h post-IV dosing F344/N rats, ~75% of the dose was detected in the feces and gut content, muscle (50% of body weight), skin (16% of body weight), liver and fat (7% of body weight) contained 12.9%, 7.25%, 4.27% and 2.99% of the dose, respectively. The tail contained 9.5% of dose indicating the entire dose was not delivered into the venous system. The remaining tissues examined, including blood, each contained <1% of the dose."

The second study is described as:

Intravenous study in F344/N rats injected with 0.9 mg/kg ^{14}C DBDPO 7.17% of administered dose was detected in the bile within 4 hours. Rate of excretion was 2.2% of the dose per hour. Metabolite identification was not carried out in this study

And qualified with:

Study details reported in a secondary source; 5.38 % of the administered dose was found in the tail indicating that the dose was delivered incompletely and an unknown amount was given through the tail vein.

We suggest the following revision to provide important details:

> "Biliary excretion of ^{14}C-DecaBDE after IV administration. Bile was collected over a 4-period following IV dosing of ^{14}C-DecaBDE to F344/N rats. Bile contained 7.2% of the dose within 4 hours. Approximately 5.38% of the dose was detected in the tail, indicating the entire dose was not delivered into the venous system. From this, a half-life elimination of the entire dose in the bile is estimated at 27.8 hrs; the actual half life is shorter due to the incomplete delivery of the dose intravenously."

Page 4-275. For consistency, the first study reported on this page regarding an oral gavage study, e.g. "Sprague-Dawley rats….", could be moved to the section on disposition after oral dosing. The citation for this study, European Chemicals Bureau,

2002 (see page 62 of that report), summarized this study as follows:

> Mörck and Klasson Wehler (2001) have investigated the metabolism of ^{14}C-labelled decabromodiphenyl ether (purity not given) using conventional and bile duct-cannulated rats. The rats were given a single oral dose of 3 µmol/kg (~2.9 mg/kg) of the test material suspended in a vehicle (a mixture of Lutrol F127, soya phospholipid and water). Excreta were collected over the following 72 hours and analysed for ^{14}C content and phenolic metabolites. The results of the study showed that the major route of excretion (~90% of the dose within 3 days) was via the feces, with only minor amounts (<0.05% of the dose) being excreted via urine. Excretion via the bile accounted for ~9.5% of the dose within 3 days. Approximated 3% of the total administered radioactivity was present in tissues 3 days after dosing and was distributed mainly in liver (~0.9%), muscle (~0.7%), skin (~0.4%), adipose tissue (~0.3%), colon wall (~0.25%), jejunum wall (~0.05%), jejunum content (~0.05%), with minor amounts (<0.05%) in plasma, kidney, heart, lung, adrenals, testis, red blood cells, thymus and spleen. More detailed analysis of the feces showed that 22%, 42% and 45% of the radioactivity present at day 1, 2 and 3 respectively was present as phenolic metabolites. In all, 8 phenolic metabolites were identified as their corresponding methy derivatives. These were dimethoxylated derivatives of penta- to octabromodiphenyl ethers (the dihydroxyl groups were always on the same ring). The remaining radioactivity present in the feces was identified as unchanged decabromodiphenyl ether.

And on page 124 and 125:

> Klasson Wehler et al. (2001) and Mörck and Klasson Wehler (2001) have investigated the metabolism of ^{14}C-labelled decabromodiphenyl ether (purity not given) using conventional and bile duct-cannulated rats. An abstract of this study is only available. Sprague-Dawley rats were given a single oral dose of 3 µmol/kg (~2.9 mg/kg) of the test material suspended in a vehicle (Lutrol F127, soya phospholipid, water). Excreta were collected over the following 72 hours and analysed for ^{14}C content and phenolic metabolites. The results of the study showed that the major route of excretion (~90% of the dose within 3 days) was via the feces, with only minor amounts (<0.05% of the dose) being excreted via urine. Excretion via the bile accounted for ~9.5% of the dose within 3 days. Approximated 3% of the total administered radioactivity was present in tissues 3 days after dosing and was distributed mainly in liver (~0.9%), muscle (~0.7%), skin (~0.4%), adipose tissue (~0.3%), colon wall (~0.25%), jejunum wall (~0.05%), jejunum content (~0.05%), with minor amounts (<0.05%) in plasma, kidney, heart, lung, adrenals, testis, red blood cells, thymus and spleen. More detailed analysis of the feces showed that 22%, 42% and 45% of the radioactivity present at day 1, 2 and 3 respectively was present as 8 phenolic metabolites. DBDPO is metabolised via oxidative debromination, as deduced from the presence of debrominated dihydroxylated diphenyl oxides, the dehydroxylation was always on one phenyl ring. Oxidation to an epoxide and further to a diol could explain the formed metabolites. Debrominated diphenyl oxides was not observed except for trace amount of three nonaBDOs.
>
> The remaining radioactivity present in the feces was identified as unchanged decabromodiphenyl ether.

The ECB 2002's summary is based on an abstract and a poster presented at a meeting, e.g.

> Klasson Wehler E, Mörck A and Hakk H (2001). Metabolism of polybrominated diphenyl ethers in the rat. Second International Workshop on Brominated Flame Retardants, May 14-16, Stockholm University, Sweden, pp 93-98.
>
> Mörck A and Klasson Wehler E (2001). Metabolism of decabromodiphenyl ether (BDE-209) in the rat. Poster presentation, Second International Workshop on Brominated Flame Retardants, May 14-16, Stockholm University, Sweden, pp291-294.

Morck and Klasson Wehler's work on DecaBDE has been published as Morck et al. 2002.[33] This publication is the preferred citation for this work, and provides details not available during development of ECB 2002.

The ECB 2002 statement that 22%, 42% and 45% of fecal radioactivity at 1, 2 and 3 days post-dosing, respectively, was present as 8 phenolic metabolites is incorrect and likely caused by using an abstract and poster as source material. Total radioactivity present in feces at 0-24, 24-48 and 48-72 hours post-dosing was 71%, 17% and 2% of the dose (Fig 3a of Morck et al. 2002). Fecal radioactivity extracted in the 'phenolic' fraction was 8%, 15% and 14% of total on each of the three days. Thus, a total of 5.68%, 2.55% and 0.28% of the dose was extracted in 'phenolic fraction' of the feces on days 1, 2, and 3 post-dosing.

Any conclusions regarding DecaBDE's 'debromination' must take into consideration the ^{14}C-DecaBDE synthesis method, which was not described in the information available to the ECB during its deliberations. Hardy et al. 2009 (page 4), citing Morck et al. 2002, reported:

> The ^{14}C-BDE-209 was synthesized from ^{14}C-phenol via 2,4-dibromophenol and tetrabromodiphenyl ether (tetraBDE). Both unlabeled tetraBDE and BDE-209 were intentionally added at different steps in the process to adjust the specific activity. The unlabeled BDE-209 was synthesized similarly to the radiolabeled compound. We note that this synthesis route is dissimilar from that used in commercial processes, which directly brominate diphenyl ether; therefore, the synthesis used by Mörck et al. (2003) may have produced a pattern of impurities unlike that of the commercial product. Results were mainly expressed on extraction characteristics and not on structural identity.

Points important to interpreting Morck et al's (2002) results include:

- The ^{14}C-test article and the unlabelled BDE 209 used to adjust its specific activity were synthesized in Morck et al.'s laboratory.
- Characterization of the lab-synthesized labeled and unlabelled DecaBDE was not reported, although both were said to be >98% BDE 209. The method used to determine purity was not provided.
- The synthesis method for both the ^{14}C- and unlabelled BDE 209 began with labeled/unlabelled phenol. Thus, phenols were potential contaminants in the test material and may have resulted in the reported detection of 'phenolic' metabolites.

[33] Morck et al. 2002. Decabromodiphenyl ether in the rat: absorption, distribution, metabolism, and excretion. Drug Metab Dispose 31:900-907.

- The synthesis method for both the ^{14}C- and unlabelled BDE 209 proceeded via tetrabromodiphenyl ether.
- Tetrabromodiphenyl ether was intentionally added during the synthesis to adjust the specific activity of the ^{14}C-BDE 209 test article.
- Because both labeled and unlabeled phenol and tetrabromodiphenyl ether were brominated during synthesis, diphenyl ethers and phenols of varying bromination levels are potential impurities in Morck et al.'s test material.

Lower brominated diphenyl ethers containing the ^{14}C-label, detected in treated rats and considered to be metabolites of BDE 209 must be distinguished from those present in the ^{14}C-test article. Morck et al. (2002) did not do this, and therefore conclusions regarding 'debromination' cannot be drawn from this study.

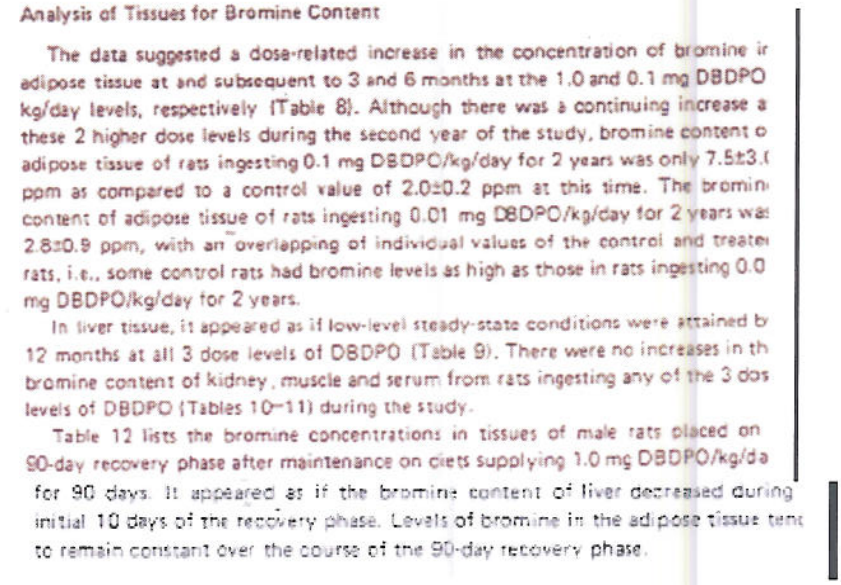
New information regarding Morck et al. (2002) has been generated subsequent to ECB 2002. Hardy et al. (2009) reviewed Morck et al.'s methods and results and determined the authors referred to certain unknowns as "phenolic" based on their extraction characteristics. Phenolic metabolites were *not* structurally identified in that study. Importantly, Morck et al. did not determine that these "phenolic metabolites" contained the ^{14}C-radiolabel, which would indicate their origin from the ^{14}C-test article. The ^{14}C-radiolabel was used exclusively to quantitate amounts in various tissues and excreta. The ^{14}C-radiolabel was *not* used to identify chromatographic peaks containing the radiolabel that could then be studied for structural identity.

The DfE document would correctly report Morck et al.'s results by deleting "8 phenolic metabolites were present in the feces" and "DBDPO was metabolized via debromination". These conclusions cannot be drawn from this work.

Page 4-275. Regarding the study cited as "Darnerud, 2001" and qualified as "Sufficient study details reported in a secondary source: the Darnerud citation is a review article. The Darnerud citation summarized the early development work of Dow Chemical Corporation as originally reported in Kociba et al (1979). Darnerud summarized this work as follows:

> In a 2-year accumulation study, rats were maintained on diets providing up to approximately 1.0 mg technical decaBDE/kg body weight (bw) per day (of which 77.4% was the decaBDE congener, 21.8% nonaBDE, and 0.8% octaBDE). Selected tissues were analyzed for total bromine content. In most tissues (serum, liver, kidneys, skeletal muscle, and testes) the bromine contents were not above background, but in the adipose tissue bromine concentration was 3-fold that of controls (0.1 mg/kg bw/day). Regarding elimination, the moderate bromine accumulation in the adipose tissue remained unaffected during 90 days of recovery, whereas bromine was cleared from the liver within 10 days of recovery (*82,83*).

The original authors of this work, Kociba et al. 1975 (pages 278 and 280), reported:



Analysis of Tissues for Bromine Content

The data suggested a dose-related increase in the concentration of bromine ir adipose tissue at and subsequent to 3 and 6 months at the 1.0 and 0.1 mg DBDPO kg/day levels, respectively (Table 8). Although there was a continuing increase a these 2 higher dose levels during the second year of the study, bromine content o adipose tissue of rats ingesting 0.1 mg DBDPO/kg/day for 2 years was only 7.5±3.(ppm as compared to a control value of 2.0±0.2 ppm at this time. The bromin content of adipose tissue of rats ingesting 0.01 mg DBDPO/kg/day for 2 years wa 2.8±0.9 ppm, with an overlapping of individual values of the control and treate rats, i.e., some control rats had bromine levels as high as those in rats ingesting 0.0 mg DBDPO/kg/day for 2 years.

In liver tissue, it appeared as if low-level steady-state conditions were attained b 12 months at all 3 dose levels of DBDPO (Table 9). There were no increases in th bromine content of kidney, muscle and serum from rats ingesting any of the 3 dos levels of DBDPO (Tables 10–11) during the study.

Table 12 lists the bromine concentrations in tissues of male rats placed on 90-day recovery phase after maintenance on diets supplying 1.0 mg DBDPO/kg/da for 90 days. It appeared as if the bromine content of liver decreased during initial 10 days of the recovery phase. Levels of bromine in the adipose tissue tend to remain constant over the course of the 90-day recovery phase.

The doses in this 2-year feeding study were 0, 0.01, 0.1 and 1.0 mg/kg bw/d. The test article was the former commercial product composed of 77.4% BDE 209, 21.8% nonaBDEs, and 0.8% octaBDEs. The lack of accumulation in liver, kidney, muscle and serum after 2 years exposure is noteworthy, and suggests that bromine from either the DecaBDE molecule or the lower brominated diphenyl ethers present in the test article did *not* accumulate in these tissues. An increase in bromine in *adipose* tissue was observed at doses of 1.0 and 0. 1, but not at 0.001, mg/kg/d.

To interpret the adipose tissue results, it is important to recognize that the analytical method was nonspecific for DecaBDE or other polybrominated diphenyl ethers. Neutron activation involves sample bombardment with neutrons, and activation of elements within the sample, in this case bromine, to radioisotopes. The radioactive emissions and decay paths of elements are well known and can be used to identify the elements present in the sample as well as their concentrations. This methodology detected the presence of *bromine,* but not the molecule to which it was attached (if any). Thus, the identity of the bromine-containing substance detected in adipose tissue is unknown, and cannot be ascribed to the DecaBDE congener. Based on known properties, octaBDEs present in the test article are likely candidates for the bromine detected in adipose at 2 years. In contrast to the test article used in this study, today's commercial DecaBDE product in use today is >=97% BDE209, and is not expected to accumulate in liver, kidney, muscle, serum or adipose.

New information on DecaBDE's disposition has been developed, e.g, Biesemeier et al. 2010[34], and should be added to the section on "Oral ADME in vivo". A summary is provided below:

[34] Biesemeier et al. 2010. Effects of dose, administration route, and/or vehicle on decabromodiphenyl ether concentrations in plasma of maternal, fetal, and neonatal rats and in milk of maternal rats. Drug Metabolism and Disposition 38(10): 1648 – 1654.

"DecaBDE levels in rat maternal plasma and milk, fetal and neonatal plasma after dosing during gestation and lactation. DecaBDE levels in plasma and/or milk determined in Sprague Dawley rat dams, fetuses and/or nursing pups after repeated gavage throughout gestation and/or lactation. Doses = 10, 100, 1000 mg/kg/d. Plasma levels in dams, fetal litters and neonatal pups were similar after repeated oral doses >= 10 mg/kg/d; maximal plasma and milk concentrations achieved at 10 mg/kg/d and did not increase with dose. Fetal plasma and maternal milk levels were lower than maternal plasma. Neonatal plasma levels were similar to or > maternal plasma. Apparent steady-state maternal plasma levels achieved within 14 daily doses. Uptake from the gut was diffusion limited and exhibited zero order uptake kinetics at doses >= 10 mg/kg/d, and perhaps as low as 2 mg/kg. First order uptake kinetics likely at doses <= 1 mg/kg/d."

This information is critical to hazard and risk assessment of DecaBDE.

Page 4-276. Property/Endpoint = Other. Two reports of detection in U.S. human breast milk are reported and attributed to EPA 2008. We recommend that information be substituted with a more recent publication of work funded by the U.S. EPA and NIEHS, Daniels et al. 2010[35]. Page 158 of that publication indicates the U.S. Centers for Disease Control is unable to measure DecaBDE in breast milk:

> We assessed variability by individual characteristics only among the congeners detected in > 70% of the participants. We were unable to measure BDE-209, the primary congener of the decaBDE formulation, which is the only brominated flame retardant still produced in the United States. BDE-209 is stable but less likely to bioaccumulate and be detected at remarkable levels in human tissue compared with the lower brominated congeners because of its short half-life (i.e., 2 weeks in humans) (Sjodin et al. 2003; Thuresson et al. 2006). According to the Agency for Toxic Substances and Disease Registry (2004), "the lower brominated PBDEs are much more likely than decaBDE to be stored in the mother's body and released during pregnancy, cross the placenta, and enter fetal tissues. Because lower brominated PBDEs dissolve readily in fat, they can accumulate in breast milk fat and be transferred to babies and young children."

Similar to its attempts with human serum, CDC has been unable to develop an analytical method for the determination of DecaBDE in human breast milk. The inability of CDC to measure DecaBDE in human breast milk raises serious questions about the validity of

[35] Daniels et al. 2010. Individual characteristics associated with PBDE levels in U.S. human milk samples. Environ Health Perspectives 118(1):155-160.

reports in the literature claiming to have detected the congener in non-exposed individuals.

Page 4-277. Carcinogenicity.

Summary. DfE rates DecaBDE as of MODERATE hazard for carcinogenicity, which is defined as "limited or marginal evidence of carcinogenicity in animals (and inadequate evidence in humans)". DfE defines LOW hazard as "Negative studies or robust mechanism-based SAR". The negative carcinogenicity study on DecaBDE (Kociba et al. 1975) was not considered by DfE.

DfE's concern for the potential carcinogenicity of DecaBDE is misplaced. The results of the 1986 US National Toxicology Program's two-year carcinogenicity studies in rats and mice are indicative of low hazard given the excessive doses, the limited evidence of carcinogenicity, lack of mutagenicity, and an earlier two-year carcinogenicity study reporting no evidence of carcinogenicity at a lower doses (Kociba et al. 1975).

DfE did not take the Kociba et al. 2-year study into consideration.

DecaBDE is not listed by the NTP as a known or reasonably anticipated human carcinogen. This is significant, because NTP conducted the two-year studies in rats and mice on which IRIS 2008 and the draft DfE document based its assessment of DecaBDE.

DecaBDE is not listed by IARC as 'known to be, should be regarded as or a cause for concern of carcinogenic to humans'. The NTP two-year studies were evaluated by IARC, which classified DecaBDE as Group 3 "not classifiable as to carcinogenicity to humans" based on "limited evidence in animals".

Page 4-278. Combined Chronic Toxicity/Carcinogenicity. NTP two year study in mice. "Equivocal evidence" of carcinogenicity in male mice should be qualified. The early loss of control male mice due to fighting impacted the numbers of tumors observed in controls at the end of the study. The Discussion and Conclusions section of NTP's 1986 report said on page 51:

> Neoplasia that occurred at significantly increased incidences in mice was limited to the

livers of male mice. Hepatocellular adenomas or carcinomas (combined) were observed in low dose male mice at a significantly greater incidence than in the controls (control, 8/50; low dose, 22/50; high dose, 18/50) (see Table 18). Thyroid gland follicular cell adenomas or carcinomas (combined) in male mice were observed at marginally increased incidences (control, 0/50; low dose, 4/50; high dose, 3/50). The significance of this lesion was supported by an increased incidence of follicular cell hyperplasia in male mice. The evidence of carcinogenicity in male mice is weakened by the early loss of control animals and the lack of a statistically significant effect at the high dose. Therefore, the increased incidence of hepatocellular neoplasms in low dose animals and the less than significant increase in thyroid gland tumors are considered equivocal evidence of carcinogenicity of decabromodiphenyl oxide in male mice.

Please add that mortality in mice was unaffected by administration of dietary doses 3,200 to 7,780 mg/kg/d for two years.

Please indicate, in addition to 25,000 ppm diet, that the LOAEL in male mice for nonneoplastic lesions was 3,200 mg/kg/day for two years. This information is important for the reader's accurate interpretation of the LOAEL.

Page 4-279. Please add that no adverse effects on food consumption or body weight were observed in rats in NTP's two-year study.

Please indicate that the systemic NOAEL and LOAEL were equivalent to 1120 and 2240 mg/kg bw/d, respectively, for two years, and the local effects LOAEL was equivalent to 1120 mg/kg bw/d.

Page 4-280. The results of the Kociba et al. 1975 two-year carcinogenicity study in rats should be added to this section, because the study provides important hazard information. This study has typically been omitted from EPA reviews (including EPA 2008) of DecaBDE due to the comparatively low doses administered. This study provides significant new information with respect to hazard and risk identification, and should be included.

The highest dose in Kociba et al. (1975) was 1 mg/kg bw/d. No evidence of toxicity or carcinogenicity was observed. This is important to hazard evaluation, since it clearly demonstrates a lifetime-no-effect-level, even when the former 77% BDE 209 commercial product was used as test article. The lack of effects observed in this study has relevance to any concern for toxicity due to metabolism of BDE 209 to lower brominated congeners. The test article administered by Kociba et al. was known to contain

significant levels of nona- and octaBDEs (Table 1) and the length of study provided ample opportunity for the generation of lower brominated congeners and expression of toxicity. No adverse effects were observed, and no appreciable accumulation was detected. The absence of effects indicates concern for toxicity due to metabolites can be disregarded. The results of this study are relevant to low environmental exposures, because of the low doses administered in the diet.

Table 1. Dietary dose of PBDE congeners present in the test article and administered in the Kociba et al. (1997) two-year study in rats due to the composition of the test article.

BDE	Test Article Composition (%)	Dietary Dose of Test Article(mg/kg/d)		
		1	0.1	0.01
DecaBDE	77.4	0.774	0.0774	0.00774
NonaBDEs	21.8	0.218	0.0218	0.00218
OctaBDEs	0.8	0.008	0.0008	0.00008

A summary is provided below:

> "2 year carcinogenicity study (diet) in Sprague-Dawley rats (25/sex/group). Doses: 0, 0.01, 0.1, 1 mg/kg bw/d. Test article: 77.4% DecaBDE, 21.8% NonaBDEs, 0.8% OctaBDEs.
>
> No effect on clinical signs, body weight, food consumption, hematology, urinalyses, clinical chemistries, organ weights, tumors or organ histopathlogy.
>
> Study details provided in Kociba et al. 1975, and European Chemicals Bureau, 2002."

Page 4-281. Reproductive and Fertility Effects Endpoint. The one-generation study results are published[36](Norris et al. 1975). The final report[37] on study is being submitted so that the data quality endpoint can be updated..

Please add that the composition of the test article was that of the 77% DecaBDE product (described elsewhere in these comments). The test article contained significant levels of nona- and octaBDEs. The absence of effects on reproduction and fertility is significant due to concern for generation of lower brominated diphenyl ether metabolites from BDE 209.

At doses administered in the study, direct exposure to Nona- and OctaBDEs in the one generation study is shown in Table 2.

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[36] Norris et al. 1975. Toxicology of octabromobiphenyl and decabromodiphenyl oxide. Environ Health Perspectives 11: 153- 162.

[37] Swartz et al. 1975. Results of a reproduction study in rats maintained in diets containing decabromodiphenyl oxide. Toxicology Research Laboratory. Dow Chemical U.S.A. APPENDIX 5.

Table 2. Dietary dose of PBDE congeners present in the test article and administered in the one-generation reproduction study in rats due to the composition of the test article.

BDE	Test Article Composition (%)	Dietary Dose of Test Article(mg/kg/d)		
		100	30	3
DecaBDE	77.4	77.4	23.22	2.322
NonaBDEs	21.8	21.8	6.54	0.654
OctaBDEs	0.8	0.8	0.24	0.24

Page 4-282. Developmental Effects. Summary. DecaBDE is rated HIGH based on "the most conservative NOAEL and LOAEL values in the located studies". DfE further commented "This aligns with the assessment for decaBDE published by EPA's Integrated Risk Information (IRIS)." In reaching this conclusion, DfE relies on out-dated information that has been superceded by new data generated from GLP/guideline-compliant developmental neurotoxicity and prenatal developmental studies utilizing the current commercial DecaBDE product as test article. DfE has no scientific justification for relying on the out-dated information derived using an invalid experimental design.

DfE's HIGH rating for this endpoint rests with developmental neurotoxicity studies in mice administered a single low oral dose on PND 3 or similarly low oral doses over PND 2-15. EPA's IRIS evaluation was based on reported effects in neonatal mice after a single low oral dose. Among other deficiencies, this experiment was not conducted according to GLPs or an established guideline, used too few animals for proper statistical evaluation, treated pups from the same litter as independent variables for statistical analysis, did not use accepted equipment for motor evaluation, and evaluated only one neurological endpoint. The experimental design used in this study is prone to producing false positives, and has been discredited. IRIS's use of this study in developing an RfD for DecaBDE has been criticized in the peer-reviewed literature.

Goodman 2009[38] performed a critical review of the available studies investigating DecaBDE and neurodevelopmental effects, and conducted a weight-of-evidence analysis to the strength of the evidence for potential neurodevelopmental effects at low doses. The same studies relied upon by DfE and IRIS in reaching a HIGH rating were reviewed. The abstract from Goodman 2009 reads as follows:

[38] Goodman J. 2009. Neurodevelopmental effects of decabromodiphenyl ether (BDE 209) and implications for the reference dose. Regul Toxicol Pharmacol 54:91-104.

On June 30, 2008, the US EPA's IRIS updated their toxicological review on the 2,2′,4,4′,5,5′,6,6′-decabromodiphenyl ether congener and published a revised oral RfD of 0.007 mg/kg day based on a NOAEL for neurobehavioral effects of 2.22 mg/kg day, as reported by Viberg, H. et al., 2003b. Neurobehavioral derangements in adult mice receiving decabrominated diphenyl ether (PBDE 209) during a defined period of neonatal brain development. Toxicol. Sci. 76, 112–120 (Comment in: Toxicol. Sci. (2004) 2079, 2205–2206, author reply 2207–2208, Comment in: Toxicol. Sci. (2004) 2081, 2528–2529)], and a total uncertainty factor of 300. To evaluate IRIS' updated RfD, we conducted a weight-of-evidence analysis of developmental neurobehavioral effects. The evidence consists of four studies from two laboratories [Viberg et al., 2003b; Viberg, H. et al., 2007. Changes in spontaneous behaviour and altered response to nicotine in the adult rat, after neonatal exposure to the brominated flame retardant, decabrominated diphenyl ether (PBDE 209), Neurotoxicology 28, 136–142; Johansson, N. et al., 2008. Neonatal exposure to decabrominated diphenyl ether (PBDE 209) causes dose–response changes in spontaneous behaviour and cholinergic susceptibility in adult mice. Neurotoxicology; Rice, D.C. et al., 2007. Developmental delays and locomotor activity in the C57BL6/J mouse following neonatal exposure to the fully brominated PBDE, decabromodiphenyl ether, Neurotoxicol. Teratol. 29, 511–520]. The reported effects from these laboratories were in opposite directions – Rice et al. (2007) found mice treated with 20 mg/kg day BDE-209 initially had higher activity and an increased habituation, while the Viberg group reported mice and rats treated with 20 mg/kg BDE-209 (Viberg et al., 2003b, 2007) or mice treated with ⩾2 mg/kg BDE-209 (Johansson et al., 2008) had lower initial activity and decreased habituation (although inappropriate statistical methods may have affected results). There was also an overall lack of effects noted in the Functional Observational Battery conducted by Rice et al. (2007). Thus, the Viberg et al. (2003b) study, even in conjunction with other studies, is not suitable for establishing an RfD for BDE-209 or the commercial decabromodiphenyl ether product.

A report from the ILSI Research Foundation/Risk Science Institute expert working group on neurodevelopmental endpoints included authors from EPA's Neurotoxicology Division, NHEERL and OPPTS (Holson et al. 2008). The report was funded in part by EPA. Regarding the experimental design used in the single dose studies (e.g. the comments on reference 16), Holson et al. (2008) said:

Finally, we add a very brief word regarding recent reports on the use of the litter as the basic unit of analysis in toxicology studies. In an excellent paper, Elswick and colleagues [15] have analyzed the effects of using 1 or more ventral prostate weights per litter on experimental outcome and power. This paper correctly used litter as a random factor in all analyses, and not surprisingly concluded that drawing ventral prostate weights from more than one pup per litter was preferable to the use of a single pup per litter. Hence this paper does not in any way question the use of the litter as the fundamental unit in analysis; it only shows that litter means based on a larger *n* are more accurate, an inarguable conclusion. A second result, published as a recent abstract [16], is more problematic. This abstract appears to report that drawing data for spontaneous motor activity from 3 mice from each of three litters and treating this as an *n* of 9 has the same power as using animals from 9 litters, evidently one animal per litter. It would appear that this was not a true Monte Carlo study, because statistically this conclusion is inaccurate, and would not be obtained in a true Monte Carlo simulation when, as is generally the case (see Table 3), there are litter effects on spontaneous motor activity (Monte Carlo analysis is a statistical method used for simulating reality that takes into account randomness by testing a very large number of scenarios).

In summary, ignoring litter effects in the statistical analysis of DNT studies is simply not an acceptable practice. Standard ANOVA models make inclusion of litter as a correlated variable straight-forward, and failures to use such models risk unacceptable levels of alpha inflation.

Williams and DeSesso (2010)[39] reviewed studies suggesting that exposure to certain substances, including DecaBDE, during the perinatal period may affect locomotor activity and/or memory and learning. The review included those studies used by IRIS in their evaluation of DecaBDE. Williams and DeSesso (2010) concluded the following as reported in the abstract of the publication:

[39] Williams and DeSesso 2010. The potential of selected brominated flame retardants to affect neurological development. J Toxicol Environ Health, Part B 13:411-448.

Various brominated flame retardants (BFR), including polybrominated diphenyl ether (PBDE) congeners, hexabromocyclododecane (HBCD), and tetrabromobisphenol A (TBBPA), are commonly used in household items and electronics and have been detected in the environment and/or the bodily fluids of people, including children. Some studies in animals suggest that exposure to PBDE congeners, HBCD, or TBBPA during the perinatal period may affect locomotor activity and/or memory and learning. Epidemiological studies showing similar effects in humans, however, are lacking. To assess whether an association exists between perinatal exposure and development of consistent neurobehavioral alterations, published animal studies investigating perinatal exposure to PBDE congeners, HBCD, or TBBPA with specific neurobehavioral evaluations—particularly, assessments of motor activity—were reviewed for consistency of results. Our analysis shows that although the majority of studies suggest that perinatal exposure affects motor activity, the effects observed were not consistent. This lack of consistency includes the type of motor activity (locomotion, rearing, or total activity) affected, the direction (increase or decrease) and pattern of change associated with exposure, the existence of a dose response, the permanency of findings, and the possibility of gender differences in response. Interestingly, Good Laboratory Practices (GLP)-compliant studies that followed U.S. Environmental Protection Agency (EPA)/Organization for Economic Cooperation and Development (OECD) guidelines for developmental neurotoxicity testing found no adverse effects associated with exposure to PBDE209, HBCD, or TBBPA at doses that were orders of magnitude higher and administered over longer durations than those used in the other studies examined herein. The lack of consistency across studies precludes establishment of a causal relationship between perinatal exposure to these substances and alterations in motor activity.

The single dose studies in neonatal mice relied upon by IRIS and DfE in reaching their conclusion regarding DecaBDE's potential for developmental neurotoxicity have been shown to be unreliable. DfE's use of this information is not scientifically justified.

New information has become available since IRIS's evaluation. A guideline/GLP-compliant developmental neurotoxicity study has been performed by an experienced toxicology laboratory using four dose levels plus a control group with administration of DecaBDE by gavage to maternal rats from GD 6 through lactation at doses up to 1000 mg/kg/d (Biesemeier et al. 2011). The NOAEL for developmental neurotoxicity in rat offspring was 1000 mg/kg/d, the highest dose tested. This was a robust study using 20 pregnant rats per dose level in order to produce sufficient pups for evaluation. The guideline-required endpoints were evaluated – growth, motor activity, auditory startle, learning and memory, neuropathology and morphometry. The abstract from the peer-reviewed publication on this study reads as follows:

BACKGROUND: Decabromodiphenyl ether (DecaBDE; CASRN 1163-19-5) is a flame retardant used in a variety of manufactured products. A single oral dose of 20.1 mg/kg administered to mice on postnatal day 3 has been reported to alter motor activity at 2, 4, and 6 months of age. **METHODS:** To further evaluate these results, a developmental neurotoxicity study was conducted in the most commonly used species for studies of this type, the rat, according to international validated testing guidelines and Good Laboratory Practice Standards. DecaBDE was administered orally via gavage in corn oil to dams from gestation day 6 to weaning at doses of 0, 1, 10, 100, or 1,000 mg/kg/day. Standard measures of growth, development, and neurological endpoints were evaluated in the offspring. Motor activity was assessed at 2 months of age. Additional motor activity assessments were conducted at 4 and 6 months of age. Neuropathology and morphometry evaluations of the offspring were performed at weaning and adulthood. **RESULTS:** No treatment-related neurobehavioral changes were observed in detailed clinical observations, startle response, or learning and memory tests. No test substance-related changes were noted in motor activity assessments performed at 2, 4, or 6 months of age. Finally, no treatment-related neuropathological or morphometric alterations were found. **CONCLUSIONS:** Under the conditions of this study, the no-observed-adverse-effect level for developmental neurotoxicity of DecaBDE was 1,000 mg/kg/day, the highest dose tested. *Birth Defects Res (Part B)* 92:17–35, 2011.

The final report on this study was submitted to EPA in 2010, and the results were published in the peer-reviewed journal, Birth Defects Research Part B, e.g. Biesemeier et al. 2011. The publication and its supplemental information have been submitted to EPA and are included in these comments as an appendix.

DfE's reliance on out-dated and inaccurate information on this endpoint is not justified. DecaBDE should be rated LOW for this endpoint.

Page 4-238. Prenatal Exposure Endpoint. The LOAEL (conceptus) should be corrected to 100 mg/kg/d. The original publication of this study in Norris et al. (1973)[40], page 205 said:

Teratology Study on DBDPO

Daily intubation, by intragastric gavage, of pregnant females on gestation days 6–15, with 1000, 100, 10, or 0 mg of DBDPO/kg, suspended in corn oil, caused no teratogenic response at any dose level. There were no indications of toxicity among the rats during gestation. The maternal body weights and food consumption of the DBDPO treated rats did not differ from control rats.

The terminal liver weights of the DBDPO treated rats, obtained at the time of cesarean section, were not different than the controls. Similarly, no differences were seen between the treated and control rats with respect to (1) the position and number of fetuses in utero, (2) the number of corpea lutea, (3) individual pup weight, crown-rump length, and male to female sex ratio. Significant incidences in resorptions occurred at the low dose levels but not at the high dose level.

No gross external abnormalities were seen in the fetuses from dams treated at any dose level of DBDPO. Soft tissue [8] and skeletal examinations [9] revealed an increased number of litters with subcutaneous edema and delayed ossification of normally developed bones of the skull of the fetuses of dams at the 1000 mg/kg level of DBDPO but not at the 100 mg/kg level.

Analysis of the maternal and fetal livers for bromine revealed statistically significant increased concentration in the livers of the maternal animals receiving 1000 mg/kg/day of DBDPO. The concentrations in maternal livers at the two lower dose levels were not different than the controls. Likewise, there was no difference in the bromine concentration in the livers of the fetuses from dams receiving any dose level of DBDPO when compared with the controls.

[40] Norris et al. 1973. Toxicological and environmental factors involved in the selection of decabromodiphenyl oxide as a fire retardant chemical. Applied Polymer Symposium No. 22: 195-219. APPENDIX 6.

Page 4-284. The original publication for this study is Hardy et al. 2002 (APPENDIX 5).

Page 4-285. Reference identified as Biesemeier et al. 2011. This endpoint should be classified as **Pre- and Postnatal Exposure**. Under Data Quality, please was a GLP/guideline-compliant study.

Page 4-286. Postnatal Exposure. The study described on this page is that of Rice et al. 2007.[41] Please see Hardy et al. 2009 and Goodman 2009 for a discussion of this publication.

The change in palpebral reflex was reported in male pups on the earliest day of assessment. Assessment of this function is only appropriate once eyes are fully open, but the percentage of pups with eyes fully open was not reported. No difference in the % of pups responding to the reflex was observed in male or female pups assessed at three later days or in female pups at the earliest day of assessment. A subjective observation of increased struggling was reported in male pups in the low dose only and only on PND20. No difference was noted in the high dose pups on that day or in any pups on PND 16 and 18. These observations are not useful for determination of an adverse effect level.

Serum T4 levels were measured on PND 21, not 70 as indicated in the DfE document. There was no statistically significant difference between treated and control T4 levels. However, the authors reported that the *slope* of a graph of serum T4 concentrations in control and treated male pups, but not female pups, was significantly different from 0. That is, the slope of the line was not horizontal. A change in slope, especially in a study consisting of only 2 treatment levels (rather than three which would allow for a proper dose-response curve), does not qualify as an adverse effect, and cannot be used to establish a LOAEL.

Statistically significant differences in locomotor activity at PND 70 between treated and control male mice were *not* reported. Rice et al. reported that the *rate of decline* in activity over the first 1.5 h of the 2-h activity session was significantly different compared to that in control male mice over this period. No difference in the rate of decline was reported for adult male mice at 1 year of age or female mice at PND 70 and at 1 year of age. With respect to locomotor activity, Hardy et al. 2009 said:

[41] Rice et al. 2007. Developmental delays and locomotor activity in the 57BL6/1 mouse following neonatal exposure to the fully-brominated PBDE, decabromodiphenyl ether. Neurotoxicol Teratol 29:511-520.

> At PND 70 and at 1 year of age, Rice et al. (2007) evaluated locomotor activity in treated and control animals. Locomotor activity was monitored based on movement episodes by 15-min time intervals over a 2-h period. In contrast to Viberg et al. (2003), no statistically significant differences in locomotor activity were reported between treated and control animals within each time interval at PND 70 or at 1 year of age. Nonetheless, for high-dose male pups at PND 70, the authors reported that the rate of decline over the first 1.5 h of the 2-h activity session was significantly different compared to the rate of decline over the same period for control animals ($p < .05$) (Table 30). No differences in the rate of decline were reported for adult male mice at 1 year of age or female mice at PND 70 and at 1 year of age (Table 31). Based on these data, the authors concluded that BDE-209 is a developmental neurotoxicant that, following neonatal exposures, can produce long-term behavioral changes (Rice et al., 2007).

The reported changes in locomotor activity and T4 levels are not suitable for use in deriving a LOAEL.

Page 4-287. Determination of NOAELs and LOAELs for the two single dose studies administered to neonatal animals described on this page is not appropriate. As discussed in comments on the Summary of this section, these studies were performed using an invalid experimental design.

Page 4-287. Neurotoxicity. Summary. The information in the Summary is identical to that of the Developmental Summary. The hazard rating for this endpoint should be based on the GLP/guideline compliant developmental neurotoxicity study (Biesemeier et al. 2011), which produced a NOAEL of 1000 mg/kg/d, administered over gestation and lactation. A rating of LOW hazard is appropriate for the reasons given previously.

Page 4-288. Developmental Neurotoxicity. This entry relates to the Rice et al. publication. Please see our comments under **Page 4-286. Postnatal Exposure.**

Page 4-289. Study attributed to EPA 2008. Please see our comments regarding the Neurotoxicity Summary where the experimental design used in this study chosen by EPA 2008 is discussed.

Page 4-289. Study attributed to Biesemeier et al. 2011. The endpoint should be classified as Pre- & Postnatal Exposure. Please indicate that this study was performed according to GLP and EPA/OECD guidelines.

Page 4-290. Study attributed to ECB 2002 and EPA 2008. Determination of NOAEL/LOAEL from this study is not appropriate. As discussed in comments on the Summary

of this section, the study was performed via an invalid experimental design. The results have been superceded by a guideline/GLP-compliant study.

Page 4-291. Repeated Dose Effects. Summary. DecaBDE is of LOW hazard with respect to repeated dose effects based on NTP 14-d, NTP 13 wk, GD 0-19 prenatal developmental, GD 6 – 19 dose range finding prenatal, GD 6 – lactation prenatal developmental neurotoxicity studies. Pharmacokinetic work additionally demonstrates DecaBDE is poorly absorbed and rapidly eliminated. EPA 2008 (page 64) observed that short-term and subchronic studies demonstrated low toxicity with NOAELs of 3,000 mg/kg/d or higher, and that DecaBDE is not bioaccumulated.

DfE assigned a MODERATE rating for repeated dose effects based on a LOAEL obtained in a 30-d feeding study using a form of the commercial DecaBDE product that has not been in manufacture or use in ca. 30 years. The test material in the 30 d study was the former 77% DecaBDE product. Today's' commercial product is >97% DecaBDE and its toxicology profile is substantially different from that of the 77% product as demonstrated in NTP's 14-d and 13-wk studies. The U.S. National Toxicology Program (NTP 1986) used test articles comparable to today's >97% DecaBDE in 14-d and 13 wk studies in rats and mice of both genders. Page 4-292 reports NOAELs in the 14-d study ranged from ~9000 mg/kg/d to ~11,000 mg/kg/d in rats and 21,000 mg/kg/d to 23,000 mg/kg/d in mice. Page 4-293 reports the 13 week studies produced NOAELs of ~3,000 to 4,000 mg/kg/d in rats and ~10,000 mg/kg/d to 11,000 mg/kg/d in mice. Both studies were correctly reported to be performed according to guidelines and in accordance with GLPs. The basis for DfE's rating on repeated dose effects is most properly based on the NTP studies. Basing DecaBDE's repeated dose assessment on an out-dated study is not scientifically justified.

DfE's commented that the subchronic effects in the 30-d study appear consistent with the observed changes in the 2-yr study at higher doses. In making this comment, DfE does not take into consideration the difference in test article composition, the lack of liver and thyroid effects in NTP's 13 week study at doses higher than those administered by Norris et al. 1973, and the enormous doses administered over a lifetime in the two year study. Attempting to draw parallels between the 30-d study and the 2-yr study is not appropriate. This comment should be deleted.

The liver and thyroid changes observed in the 1973 study were not adverse. The liver changes are consistent with hepatic enzyme induction, and is likely due to the substantial content of lower brominated diphenyl ethers in the test article coupled with a dose of 800 mg/kg/d. Hepatic enzyme induction is an adaptive, not adverse, change. The thyroid change – hyperplasia – is consistent with a rodent-specific mechanism of action, e.g. increased elimination of thyroid hormone due to hepatic enzyme induction, and subsequent increase in hormone production by the thyroid. Thyroid hyperplasia in response to decreased circulating thyroid hormone is a normal physiological response. Rodents are sensitive to this effect, while humans are not, due to differences in thyroid hormone binding proteins.

The original publication of this study, Norris et al. 1973, page 200-01, reports the following:

30-Day Rat Dietary Feeding Studies on OBBP and DBDPO

Male Sprague Dawley rats maintained on diets containing 1.0, 0.1, 0.01, or 0% OBBP or DBDPO providing approximate doses of 800, 80, 8 or 0 mg/kg/day showed no overt indication of toxicity during the 30 day study. Inclusion of OBBP or DBDPO at any level in the diets did not influence the food consumption or body weight gains of the respective experimental animals. Hematology studies conducted during the terminal week of the study showed statistically significant decreased packed cell volume and total red blood cell count of rats on the 1% dietary level of OBBP. The hematology studies on OBBP were extended to include the rats on the 0.1 and 0.01% dietary levels. The hematological determinations of these rats and of rats receiving diets containing 1.0% DBDPO were not statistically different than the rats on the control diet.

Urinalyses made during the terminal week of the study showed no difference in total solids, pH, sugar, albumin, occult blood, and ketones of rats on diets containing OBBP or DBDPO when compared with rats on the control diet.

A comparison of organ weights showed no dose-related statistical difference in heart, testes and brain from rats on diets containing OBBP or DBDPO or in the weight of kidneys from rats on diets containing DBDPO. Enlarged livers were found in the rats on all dietary levels of OBBP and those rats on the 1.0 and 0.1% levels of DBDPO. Increased kidney weights were found in rats on diets containing 1.0 and 0.1 OBBP.

Gross pathological changes that were observed at necropsy were limited to dose related liver enlargement in rats at all dose levels of OBBP and those on the 1.0% dietary level of DBDPO. Kidney changes, consisting of petechial hemorrhage, enlargement, and mottling, were noted only in some of the rats on diets containing OBBP.

The histopathological examination of organs and tissues of the rats on the experimental diets revealed liver and kidney lesions at all levels of OBBP and at the 1.0% dietary level of DBDPO. The liver lesions consisted of centrilobular cytoplasmic enlargement and vacuolation and the kidney lesions consisted of hyaline degenerative cytoplasmic changes. The other dose related pathological finding was thyroid hyperplasia which was observed in rats on all levels of OBBP and those rats on the 1.0 and 0.1% dietary levels of DBDPO.

In utilizing the results of tests on the early 77% DecaBDE product to derive a MODERATE concern, DfE is doing so in opposition to the heavily cited EPA 2008 and EU 2002 Risk Assessment. DecaBDE's EU Risk Assessment properly recognized the NTP work as the most appropriate for assessing repeated dose effects. An assessment of DecaBDE potential for adverse effects in repeated dose studies is properly based on the NTP 14-d and 13-wk the repeated dose studies is recommended. Clearly, a substance which produces NOAELs of >20,000 mg/kg/d in mice and >9000 mg/kg/d in rats in a 14 d study as indicated in the DfE draft is of LOW hazard.

EPA 2008 did not include the 30-d study in its assessment of DecaBDE, and reference to it should be corrected. The study was performed using a highly impure form of the DecaBDE product that has not been in commercial production for over 20 years. The results are superceded by NTP's 14-d and 90- studies. Deleting the 30-d study from DfE's review is recommended.

Page 4-294. The entry on this page describes a 28 d dietary study. The study is not mentioned in EPA 2008, but was included in the EU Chemicals Bureau 2002. EU Chemicals Bureau 2002 gives the reference as "Great Lakes 1977". The EU Chemicals Bureau 2002 does not indicate that this was a guideline study, but does state that the purity of the test article is unknown. The study is unpublished. We recommend deleting this entry, because quality studies performed at higher doses for longer periods of time using characterized test material are available. In all likelihood, this study actually is the 28 d study performed by The Dow Chemical Company and reported in the Norris et al. publications.

Page 4-297. Please add to the study reporting on 4-d administration to female Long Evens rats that in addition to no effects on body weight, liver weight or T3 or T4 levels that the commercial DecaBDE product had no effect on TSH levels. The reference is Zhou et al. 2001 Tox Sci 61, 76-82. This information is also important for the Endocrine section. Note that the study authors included Ross, DeVitto and Crofton of the U.S. EPA.

Page 4-298. Endocrine Activity. Summary. The summary should be revised to reflect the very low conversion of DecaBDE to metabolites; see comments under Bioaccumulation. The lack of developmental, reproductive and adverse effects observed in repeated dose studies argues against an effect on the endocrine system.

Data. The Zhou et al. (2001) entry, and the lack of effect on TSH levels, should be included in this section. The Zhou et al. study is directly relevant to this endpoint.

The Kociba et al. (1997) results should also be included in this section. The two-year feeding study at doses of 0.01 to 1 mg/kg/d to rats produced no effects on organs of the endocrine system, despite presence of significant amounts of nona- and octaBDEs in the test material.

Including the "Maine, unpublished" information in this section is questionable. The study is said to be on-going, and therefore definitive results are not available. The year in which the study was known to be on-going should be provided. The study referred to is likely that of Rice et al. (2007), which has been completed. No statistically significant difference was observed in PND 21 serum T4 levels in male or female mice pups administered DecaBDE at 6 or 20 mg/kg/d from PND 2-15. In contrast, Rice et al. (2007) reported that the slope of the linear function for male pups in the treated versus control group was significantly different from 0. That is, a graph of the control, and two dose groups' PND21 T4 levels had a negative slope, but no statistical difference was detected between treated and control male mice. The difference in slope has been construed as an adverse effect on T4. It is not an adverse effect because no significant difference was found between control and treated T4 levels, and use of only 2 dose levels does not allow a true dose-response curve.

Page 4-301. Terrestrial Ecotoxicity. Inclusion of the chicken embryo LD50 is questionable. This is not a known endpoint for EPA's DfE SLHA, and the method of administration is not relevant to wild birds. The reported LD50 is unlikely to be achieved

in wild bird eggs given DecaBDE's low systemic bioavailability. If included, it should be clarified that the study was performed by egg injection, and not by dietary exposure.

The final report of the guideline/GLP-compliant earthworm survival and reproduction study[42] is being submitted.

The final reports of the guideline/GLP-compliant studies of DecaBDE's potential to affect terrestrial plants[43] and sludge bacteria[44] are being provided, and are recommended for inclusion. The NOEL in six terrestrial plant species for seedling emergence and growth was 6250 mg/kg dry soil, the highest dose tested. The NOEL in a limit test of sludge bacteria respiration inhibition was 15 mg/ml. This data demonstrates DecaBDE's lack of toxicity in two additional trophic levels, and therefore is important in hazard identification.

Page 4-301. Environmental Fate. Transport. Summary.

The comment that DecaBDE is expected to have moderate potential for volatilization from surface water, based on modeling, is unlikely to represent DecaBDE's environmental behavior. DecaBDE has negligible solubility in water, negligible vapor pressure, and high binding to particulates. DecaBDE's negligible water solubility will produce minimal amounts in surface water. Its high particulate binding will further limit amounts in water, as well as limiting volatilization. Its negligible vapor pressure minimizes amounts moving into air. In the atmosphere, DecaBDE is unlikely to be present in the vapor phase due to its low vapor pressure and high particulate binding. The results of the modeling program do not fit expectations for this substance or results from earlier versions of the program, and thus the modeling results are questionable.

The version of EPI used in all estimations should be provided.

Page 4-301. Henry's Law Constant. The Data Quality column indicates the HLC was estimated using measured vapor pressure and water solubility. The measured values used in the estimation should be included.

Page 4-302. Persistence. Summary. We suggest this summary section could be improved with the following additions (in italics):

"Non-guideline experimental studies indicate decabromodiphenyl ether *may be* capable of undergoing *limited* anaerobic biodegradation; however the removal rate also suggests very high persistence.", and

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[42] Aufderheide et al. 2001. Effect of decabromodiphenyl oxide on the survival and reproduction of the earthworm, Eisenia fetida. ABC Laboratories, Inc., Columbia, MI and Wildlife International, Ltd, Easton, MD. APPENDIX 7,

[43] Porch and Krueger. 2001. Decabromodiphenyl oxide (DBDPO): A toxicity test to determine the effects of the test substance on seedling emergence of six species of plants. Wildlife International, Ltd., Easton, MD. APPENDIX 8.

[44] Schaefer and Siddiqui. 2001. Decabromodiphenyl oxide (DBDPO): An activated sludge, respiration inhibition test. Wildlife International, Ltd., Easton, MD. APPENDIX 9.

"Experimental data indicate that decabromodiphenyl ether *may undergo* photolysis to *debrominated transformation products; however the majority of reaction products are unidentified, and DecaBDE's potential for photolysis is matrix-dependent."*

The final sentence should be revised by deleting "and metabolism" should be deleted. Metabolism is not relevant to environmental persistence, and, as discussed in other sections of these comments, the extent of DecaBDE metabolism is extremely low.

The final sentence should be clarified that laboratory studies, which indicate significant photolysis of DecaBDE, were performed in organic solvents. Such studies are not relevant to DecaBDE's environmental degradation. Studies of PBDEs adsorbed to house dust and exposed to sunlight indicated a decrease in the total PBDE content; decline in congeners associated with the DecaBDE product declined by ~2.5% - 4%.[45] UVA irradiation of automobile dust containing DecaBDE did not result in photolysis.[46] No evidence for the photolytic degradation of DecaBDE was observed in soil last amended with PBDE-containing sewage sludge twenty years previously.[47]

Page 4-303. Volatilization Half-life for Model River. Please see our comments under the Transport section.

Page 4-303. Aerobic soil. Please add:

Nyholm et al (2010) reported no biodegradation of BDE 209 in aerobic or anaerobic soil over a 160 period. A half-life of > 360 or 400 d was estimated.[48]

Liu et al. (2011)[49] reported no degradation of BDE 209 was observed in aerobic soil over a 180 d period.

Sellstrom et al. (2005) collected soil from 3 research stations (reference plots and sewage-sludge-amended plots) and 2 farms (reference and amended/flooded soils) in Sweden. [BDE209] in background (reference) soils ranged from 0.015 -0.75 ng/g dw, except for 1 farm which was impacted by river sediment flooding was 1.9 ng/g dw. At the 3 research stations which had been amended with sewage sludge, the concentrations ranged from 0.028 -1.0 ng/g dw. One farm where sewage-sludge had been applied had [BDDE209] of 2200 ng/g dw. The other farm which was periodically flooded by the

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[45] Stapleton and Dodderd. 2008. Photodegradation of decabromodiphenyl ether in house dust by natural sunlight. Environ Toxicol Chem. Feb;27(2):306-12.

[46] Lagalante et al. 2011. Levels of polybrominated diphenyl ethers (PBDEs) in dust from personal automobiles in conjunction with studies on the photochemical degradation of decabromodiphenyl ether (BDE-209). Environment International 37:899-906.

[47] Sellstrom et al. 2005. Effect of sewage-sludge application on concentrations of higher-brominated diphenyl ethers in soils and earthworms. Environ Sci Technol 39(23): 9064-70.

[48] Nyholm et al. 2010. Biodegradation kinetics of selected brominated flame retardants in aerobic and anaerobic soil. Environ Poll 158:2235-2240.

[49] Liu et al. 2011. Effect of decabromodiphenyl ether (BDE 209) and dibromodiphenyl ether (BDE 15) on soil microbial activity and bacterial community composition. J Haz Mat 186:883-890.

River Visken, which received effluents from textile industries, had [BDE209] of 350 ng/g dw. The farm with the highest [BDE209] had last received sludge application 20 yr prior to sampling. The authors concluded there was no evidence of photolytic breakdown of BDE209, based on the spoil chromatograms, and commented that this was in contrast to their previous work indicating photolytic debromination of BDE209 applied "artificially to soil with solvent in laboratory and field experiments" (Soderstrom et al. 2004). Further, laboratory experiments with the high-BDE209-soil showed no change in peak patterns with the length of UV exposure. The authors indicated soil ageing has been shown to encapsulate and shield contaminants thereby reducing microbial, and probably sunlight, breakdown. The fact that the soils were plowed under was also thought to impact sunlight exposure. **The authors concluded, "The results with soils collected in the field show the importance of following up laboratory studies with field studies."** Although microbial degradation was not specifically studied, as there was no evidence of *photolytic* degradation to lower brominated congeners, a similar conclusion can be reached for microbial degradation.

Page 4-303. Soil. Anaerobic Biodegradation. Please indicate that the 32-week anaerobic degradation study was performed under GLPs and according to OECD guideline. A copy of the final report on this study[50] is being provided.

Additional information should be added to the study attributed to "Illinois EPA 2007 citing Gerecke et al. 2006". Gereke et al. 2006[51] incubated DecaBDE in sewage sludge for 215 d. This can be compared to the typical holding time in an anaerobic sewage digester of ca. 30 d, and the required length for guideline anaerobic sewage sludge studies of 60 d. Due to the study's duration, Gereke et al.'s claim of degradation is irrelevant to operating anaerobic digesters.

Gerecke et al. reported DecaBDE's concentration remained unchanged after 114 days of incubation. However, the presence of nona- and octaBDEs typically present in small amounts in commercial DecaBDE products in the sludge led the researchers to conclude that a maximum of 2% of the DecaBDE could possibly have degraded over 114 days. By the end of the study, DecaBDE's concentration had declined by 30%, but only ca. 5% was represented in the form of lower brominated diphenyl ethers. This data does not suggest anaerobic digesters convert BDE 209 to lower brominated diphenyl ethers.

The study attributed to "Illinois EPA, 2007 citing Nies et al. 2005" could not be located in a literature search. It is likely that this refers to Tokarz et al. 2008[52]. The mole fraction distribution (Fig 6; reproduced below) after 3.5 years indicates the total amount of presumed metabolites with <= 9 bromine atoms represented < 3% of the starting BDE 209. This is insignificant, especially given the duration of this study.

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[50] Schaefer and Flaggs. Potential for biotransformation of radiolabeled decabromodiphenyl oxide (DBDPO) in anaerobic sludge. Wildlife International, Ltd. Easton, MD. APPENDIX 10.

[51] Gereke et al. 2006. Gerecke et al. 2006. Anaerobic degradation of decabromodiphenyl ether. Environmental Sci Technol 39:1078-83.

[52] Tokarz et al. 2008. Reductive debromination of polybrominated diphenyl ethers in anaerobic sediment and a biomimetic system. Environ Sci Technol 42:1157-1164.

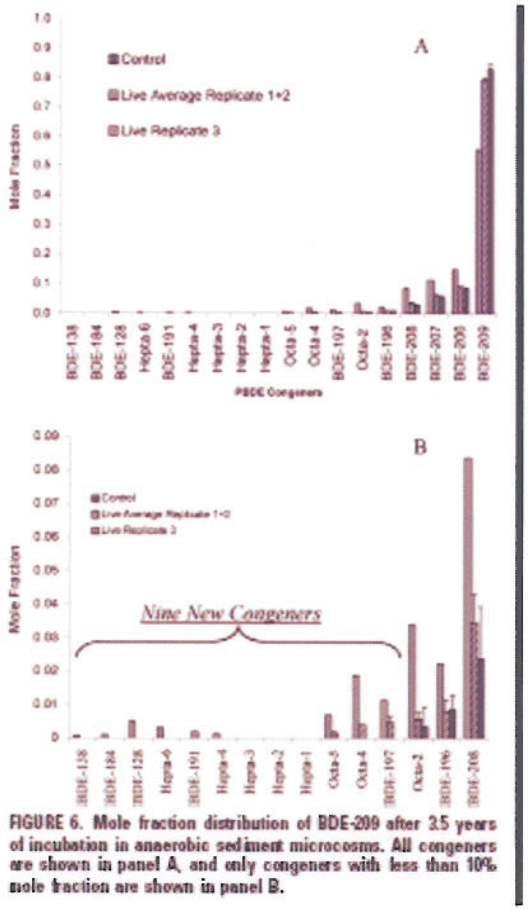

FIGURE 6. Mole fraction distribution of BDE-209 after 3.5 years of incubation in anaerobic sediment microcosms. All congeners are shown in panel A, and only congeners with less than 10% mole fraction are shown in panel B.

The study attributed to "Illinois EPA, 2007 citing Skoczynska et al. 2005" is described to report "Rapid breakdown to nonaBDEs in anaerobic sediment cultures in the presence of organic solvents (measured)" and to be "Reported in a secondary source with limited study details". The Skocyznska reference could not be located in a literature search. "Rapid breakdown" of DecaBDE is not expected, and contrary to all other studies on this material. The relevance of organic solvents to environmental sediments is not known. The entry should be deleted.

Page 4-304. Reactivity. Photolysis. DecaBDE's potential for photodegradation as well as the degradants produced is highly dependent on the matrix. This should be clearly indicated in the DfE document.

Lagalante et al. (2011) reported "Laboratory photochemical studies were conducted on both automobile dust collected from personal vehicles as well as BDE-209 adsorbed to sodium sulfate. No significant degradation occurred in the personal vehicle dust after 56 days of constant UVA irradiation while significant degradation did occur with BDE-209 adsorbed to sodium sulfate", and "After 56 days of constant irradiation under a solar

simulator, neither a significant change in the BDE-209 levels nor the other twenty monitored PBDE congeners was observed using dust from a personal vehicle".

Stapleton and Dodder (2008) reported on sunlight photolysis of PBDEs, including DecaBDE, adsorbed to house dust. Exposure of house dust to sunlight decreased the *total* PBDE content to ~77% of that present at t_0. Most of the loss of PBDEs was due to processes other than photolysis to lower brominated diphenyl ethers. The magnitude of loss similar in spiked and natural dusts. After 200 hours exposure to sunlight, congeners associated with the DecaBDE commercial product were ~ 4% (spiked dust) or ~2.5% (natural dust) lower than at t_0.

Sellstrom et al. (2005) collected soil from 3 research stations (reference plots and sewage-sludge-amended plots) and 2 farms (reference and amended/flooded soils) in Sweden. [BDE209] in background (reference) soils ranged from 0.015 -0.75 ng/g dw, except for 1 farm which was impacted by river sediment flooding was 1.9 ng/g dw. At the 3 research stations which had been amended with sewage sludge, the concentrations ranged from 0.028 -1.0 ng/g dw. One farm where sewage-sludge had been applied had [BDDE209] of 2200 ng/g dw. The other farm which was periodically flooded by the River Visken, which received effluents from textile industries, had [BDE209] of 350 ng/g dw. The farm with the highest [BDE209] had last received sludge application 20 yr prior to sampling. The authors concluded there was no evidence of photolytic breakdown of BDE209, based on the spoil chromatograms, and commented that this was in contrast to their previous work indicating photolytic debromination of BDE209 applied "artificially to soil with solvent in laboratory and field experiments" (Soderstrom et al. 2004). Further, laboratory experiments with the high-BDE209-soil showed no change in peak patterns with the length of UV exposure. The authors indicated soil ageing has been shown to encapsulate and shield contaminants thereby reducing microbial, and probably sunlight, breakdown. The fact that the soils were plowed under was also thought to impact sunlight exposure. **The authors concluded, "The results with soils collected in the field show the importance of following up laboratory studies with field studies."**

Page 4-305. Bioaccumulation. Summary. DfE indicates DecaBDE has a HIGH potential for bioaccumulation based on estimated BAF values and reports of its detection in higher trophic level organisms. DecaBDE's presumed degradation, transformation and metabolism products, e.g. lower brominated diphenyl ethers, were also said to contribute the HIGH hazard designation and to have been detected in monitoring studies.

As discussed below, the estimated BAF was obtained using faulty methodology. Laboratory studies administering known amounts of BDEs have demonstrated DecaBDE has a LOW potential for accumulation. A LOW potential for accumulation of presumed lower brominated diphenyl metabolites has also been demonstrated.

Comments with respect to environmental monitoring are provided in the following section.

The former commercial OctaBDE and PentaBDE products contained a range of PBDE congeners, including those ascribed by DfE as DecaBDE metabolism/transformation. The literature is in general agreement that the main lower PBDEs detected in environmental matrixes, e.g. BDE 47, 99, 100, 154, 153, originated from the Octa- and PentaBDE products.

Based on experimental studies, DecaBDE has a LOW potential for bioaccumulation.

Fish BCF Endpoint. The study cited for this endpoint was referenced as MITI 1998 and included a notation that the study may have been performed above the water solubility of the test substance. New information is available on this study.

The notation regarding possible conduct above the water solubility was derived from Argot's database, e.g."BCF NonIonic Training Set": BCF NonIonic Regression Data Set, BCF Validation DataSet, and BCFWin-DD_Source_Oct2008. However, the BCFWin-DD_Source_Oct2008 contains errors with respect to DecaBDE; a copy of the original entry with corrections is provided in APPENDIX 11.

Correcting the MITI study for water solubility is not appropriate. The water concentrations used in the MITI test (6 and 60 ppb) were multiples of the water solubility reported in the Norris et al. 1973, 1974, 1975 publications, e.g. 20 - 30 ppb. That water solubility is that of the early DecaBDE product, which was composed of 77% BDE209 with the remainder being nona- and octaBDEs, and correctly reflects that of the material used in the 1977 MITI test (see the summary obtained from the Japanese institution responsible for the study's conduct) e.g. >75% DecaBDE, ca 17% nonaBDEs and ca. 0.8% octaBDEs (APPENDIX 12). The test concentrations used in MITI test were within a factor of 2-3 of the water solubility of the 77% DecaBDE commercial product. A correction for water solubility is not indicated, and the notation should be deleted. The Arnot database should be corrected to reflect this.

A further correction in the Arnot database is indicated. MITI tests are performed until steady state is reached; thus, an exposure duration comment is not indicated. (That comment originated in the EU Risk Assessment discussions where some felt exposure durations should be many months. The author of these comments participated in DecaBDE's EU risk assessment.) The appropriate Log BCF Exptl and Revised Log BCF are <0.699 and <1.698, based on the actual data, and not 3.38 as shown in BCFWin-DD_Source_Oct2008. These inaccuracies in the representation of DecaBDE's data are carried over into the BCF NonIonic Regression Data Set file.

BAF Endpoint. DfE reports an estimated BAF of 49,000 based on an EPI estimate. The version of EPI used to create this estimate, and any values entered into the program prior to the calculation should be stated. Providing the EPI version used for estimations in the text of ca. 800 page DfE document is not sufficient.

A BAF of 49,000 is inconsistent with measured values determined in experimental studies administering known doses of DecaBDE. The 49,000 BAF is inconsistent with

EPA 2008 (page 64) that concluded DecaBDE does not bioaccumulate (page 64, and appears improbable for a substance that is poorly absorbed, has a low systemic bioavailability, is rapidly eliminated, and laboratory data demonstrate is not bioaccumulative.

The 49,000 BAF value is apparently based on the Arnot-Gobas model with a user-entered Log Kow of 6.27 (page 4-271 and Table 3 below). EPI 4.0 with a user-entered Log Kow of 6.27 estimates BAFs of 48,630 (upper trophic) to 95,490 (lower trophic) and up to 4,675,000 when the biotransformation rate is set to zero (estimate performed 9/11/2012). In contrast, using the EPI-generated log Kow, EPI 4.0 estimates DecaBDE's BAF to be 7-13 when biotransformation rate estimates were included, but 3,361 assuming a biotransformation rate of zero (estimate performed 9/11/2012). Thus, DecaBDE's estimated BAF is highly dependent on the Log Kow used by the software, and the biotransformation rate used in the estimation.

Table 3. Comparison of BCF and BAF estimates derived from EPI 4.0 using varying Log Kows.

Log Kow	Bioconcentration Factor	Whole Body Primary Biotransformation Rate Estimate for Fish (Arnot-Gobas)		
		Rate Constant	BCF Estimate	BAF Estimate
12.11	42*	0.04	0.9	7 – 13
		0	1.5	3,361
6.27	6367**	0.04	3,652 – 5,475	48,630 – 95,490
		0	20,590	4,675,000

* Equation used to make BCF estimate: Log BCF = -0.49 log Kow + 7.554
**Equation used to make BCF estimate: Log BCF = 0.6598 log Kow – 0.333

The estimated BCF is similarly highly dependent on the Log Kow used by the estimation program. The estimated BCF for DecaBDE is 42 based on an EPI-estimated log Kow, but 6,367 when a log Kow of 6.27 is entered. The Arnot-Gobas model estimates BCFs of 0.9-1.6 (EPI-estimated Log Kow), and 3,652 – 20,000 using an entered Kow of 6.27.

The extremely high BAFs estimated by the Arnot-Gobas model appear improbable for a substance that is poorly absorbed, has a low systemic bioavailability, is rapidly eliminated, and is not bioaccumulative in laboratory studies.

A fundamental problem with using biotransformation rates to estimate DecaBDE bioconcentration or bioaccumulation factors is that DecaBDE's elimination is not based on metabolism. DecaBDE has very poor systemic bioavailability. Only a small fraction of an oral dose is absorbed from the gut; the majority of an oral dose passes out of the gastrointestinal tract with the feces without prior absorption. The small fraction that is absorbed from the GI tract is routed to the liver. The majority of this small, absorbed fraction of the oral dose is transported directly into the bile as the parent molecule. A small portion is circulated systemically, extracted by the liver on subsequent passes and eliminated in the bile as the parent molecule. DecaBDE's elimination is not reliant on biotransformation. Thus, estimating its potential for bioaccumulation on

biotransformation is not valid. The Arnot/Gobas model does not provide a realistic estimate of DecaBDE's potential for accumulation, and should not be used for this substance.

A further problem in using the Arnot/Gobas model lies with the study on which DecaBDE's biotransformation rate was based, Tomy et al. 2004[53]. Tomy et al administered multiple polybrominated diphenyl ether (PBDE) congeners simultaneously to fish via the diet. In that study, juvenile lake trout were fed diet containing 13 different PBDE congeners, including DecaBDE, for 56 days, and untreated diet for 112 d. The dietary concentrations (per congener) were 0, ~2.5 and ~25 ng/g. This study design makes it impossible to determine the fate of individual congeners. Changes in concentrations of various PBDE congeners cannot be ascribed to DecaBDE metabolism using that study design. As correctly noted by Huwe et al. 2008[54], simultaneously administering a mixture of PBDEs "makes it impossible to determine whether debromination of any individual congeners has occurred". Finally, it is worthwhile noting that Tomy et al. reported DecaBDE's assimilation efficiency, e.g. the ratio of concentrations in fish to that in food, to 0.3% (page 1499), and its biomagnification factor 0.3. These values do not correlate with the BAFs estimated by the Arnot-Gobas model.

In addition to the problem of simultaneous administration of multiple congeners, the recovery, accuracy and precision of all dosing and measurements would have to be exact in order to confidently detect changes due to biotransformation. There is no information indicating this was the case. Further, no compositional information on the test article was provided; "Technical grade BDE-209" was used to fortify food, and was obtained from Great Lakes Chemical Corporation (Indianapolis, IN).

Additional laboratory studies demonstrate a similar low bioaccumulation or bioconcentration of DecaBDE (Table 4). These studies demonstrate the Arnot/Gobas model is not predictive of DecaBDE's potential for bioconcentration or bioaccumulation. The Arnot/Gobas model should not be used to estimate BAFs or BCFs for DecaBDE.

A final point rests with user entry of DecaBDE's measured Log Kow, e.g. 6.27, in the estimation software. The BAF/BCF estimates produced with the user entered Log Kow 6.27 clearly do not reflect those derived in laboratory tests with live animals. This is because DecaBDE's absorption, distribution and elimination are *not* driven by its Log Kow. DecaBDE's solubility in octanol versus water is not the sole contributor to its uptake and elimination from biological systems. This has not been recognized in much of the published literature on DecaBDE. The best estimate of DecaBDE's potential for bioconcentration (BCF=42) is derived without user-entered data.

Metabolism in Fish Endpoint. The DfE document summarizes Noyes et al. (2011) and indicates metabolism in juvenile fathead minnows (e.g. a range of penta- to octaBDEs

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[53] Tomy et al. (2004). Bioaccumulation, biotransformation, and biochemical effects of brominated diphenyl ethers in juvenile lake trout (Salvelinus namaycush). Environ Sci Technol 38:1496-1504.

[54] Huwe *et al.* (2008). Comparative absorption and bioaccumulation of polybrominated diphenyl ethers following ingestion via dust and oil in male rats. Environ Sci Technol. Published on Web 02/21/2008.

with 2,2,4,4,5,6-HexaBDE being most prevalent) and accumulation after 28-d dietary administration of 9.8 ug DecaBDE/g food (fed at a rate of 5% bw/d). However, the amount of DecaBDE detected in fish does not reflect bioaccumulation.

As reported by Noyes et al. (2011), the cumulative dose was ~429 ng BDE209/fish (page 269, 1st column). Page 268, 1st column states that BDE 209 accumulation was 488 ng/g ww at day 28, which refers to the amount of BDE 209 detected in the 36 – 45 fish sampled each day. This value does not refer to the amount of BDE 209 detected in *each* fish, rather it reflects the amount of BDE 209 detected in all the fish analyzed that day. Using the cumulative DecaBDE dose/fish (429 ng), the cumulative dose to all fish analyzed on day 28 was 15,444 or 19,305 ng, e.g. 429 ng/fish x 12-15 fish/tank x 3 tanks/d. DecaBDE's bioaccumulation factor, calculated as the ratio of the amount in fish at day 28 to the total dose administered, is 0.03 to 0.02 (Log BAF –1.52 to –1.69). This is not indicative of bioaccumulation.

Noyes et al. can also be used to address bioaccumulation of BDE 209 plus its presumed metabolites, e.g. lower brominated diphenyl ethers. The sum of the PBDEs present in fish analyzed at day 28 equaled ca. 976 ng, e.g. 429 ng in the form of BDE 209 plus ~ 495 ng other PBDE congeners estimated from Fig 1, page 268. The bioaccumulation factor, calculated as the ratio of all PBDEs in fish at day 28 was 0.063 – 0.05 (976 / 15,444 or 976 / 19,305). A BAF of 0.063 to 0.05 does not indicate bioaccumulation.

The amounts of purported metabolites, ca. 495 ng, represents 3.2% or 2.5% of the total DecaBDE dose administered over 28 d. Typically, identification of an individual metabolite is considered unnecessary from a toxicology or pharmacology standpoint if present at < 10% of the dose. The *total* amount of presumed metabolites in the study was <= ca. 3%. Continued concern for the accumulation or identity of DecaBDE metabolites is not justified.

The 2,2,4,4,5,6-HexaBDE congener was detected at 1.3% of the cumulative dose. Specific mention of this low level metabolite is not indicated despite being the 'predominant' metabolite. The amount detected was insignificant.

The DfE document should be corrected to reflect the calculated BAF, and that while DecaBDE was detected after 28 days of dosing, the levels of that congener and its purported metabolites do not indicate bioaccumulation.

Whether the low amounts of lower brominated diphenyl ethers detected in these studies is due to metabolic debromination or some other process should be considered.

Table 4. Laboratory studies investigating bioconcentration or bioaccumulation in fish, annelids, and rodents.

Fish				Other Biota	Reference
BCF_{water}	BAF_{diet}	BMF	Uptake from Diet		
<0.3 – 3 6 wks					Japan CSCL Database: http://www.safe.nite.go.jp/jcheck/english/template.action Test material composed of > 75% BDE 209, ca 17% nonaBDEs, ca. 0.8% octaBDEs
			0.005% 120 d		Kierkegaard et al. 1999 Environ Sci Technol 33:1612-1617 Dose = 7 or 10 mg/kg/d
			0 90 d		Stapleton et al. 2004 Envrion Sci Technol 38:112-119 No measurable uptake over 90 d; dose = 940 ng/fish/d
	0.0039		0.39% 112 d		Stapleton et al. 2006 BAF based on cumulative DecaBDE dose and total PBDE reported in fish
		0.3	0.3% 56 d		Tomy et al. 2004. Environ Sci Technol 38:1496-1504
	~0.02 28 d				Noyes et al. 2011 Tox Sci 122:265-274
				L. variegates 28 d; dose ~ 300 ug/g dry soil. Not detected in worms exposed to biosolids; < LOQ exposed via spiked sediment	Ciparis and Hale 2005 Environ Toxicol Chem. 2005 24:916-25. Commented that bioaccumulation not observed in trout or carp exposed via treated diet (e.g. Kierkegaard & Stapleton studies)
				E. fetidae 28 d; doses 312 – 5000 mg/kg dry soil. Not detected	Aufterheide et al. 2001; GLP/guideline study
				Rat BAF = 0.05 for 21 d dietary exposure	Huwe and Smith 2007 Environ Sci Technol 41:2371-2377; Additions and Corrections 41:4486.
				Rat BAF = 0, 0.06, 0.61 or 0.14 depending on dose & matrix for 21 d dietary exposure	Huwe et al. 2008 Environ Sci Technol 42:2694-2700
				Rat. BAF=0. Not detected in fat or carcass; <= 1% dose in liver; 21 days dietary exposure	Huwe et al. 2008 Environ Sci Technol 42:7018-7024
				Rat BAF rough estimate 0.00007 based on plasma concentration (~1000 ng/g ww) after 15 daily doses of 1000 mg/kg/d	Biesemeier et al. 2010 Drug Metab Dispo 38:1648-1654

Page 4-305. Environmental Monitoring and Biomonitoring. Summary. The DfE document states that DecaBDE has been reported in a variety of environmental matrixes. This is correct. However, it is not apparent that all, or even many, of its reported detection are reliable. The majority of these reports relied on detection of the bromide and/or the phenoxybenzene ion using GC/MS. Monitoring for DecaBDE's molecular ion has not been utilized in these reports. Therefore, reports relying on detection on bromide or phenoxybenzene are not specific for the detection of DecaBDE.

DecaBDE's analysis is extremely challenging, particularly when attempting to quantitate trace levels in environmental samples containing a multitude of unknown substances.[55,56,57,58,59,60,61,62,63] Reviews of the challenges associated with DecaBDE analysis are provided in Kolic et al. (2009)[64] and Hites (2008)[65].

Kolic et al. (2009) stated that as late as 2007, analysis of BDE 209 in environmental samples was not under control. Kolic et al. listed factors contributing to this lack of control: high molecular weight, elevated melting point, poor solubility even in organic solvents, significant background in buildings and laboratories. Citing others, Kolic et al. stated that as of 2002, only 14% of environmental monitoring studies reported BDE 209 and between 2002 and 2007 many labs were still not reporting BDE 209 and **none had reported results for BDE 209 monitoring the molecular ion with GC-HRMS.** Thus, reported detection and concentrations of BDE 209 in environmental matrixes should be viewed skeptically.

Note that Hites stated regarding reports of detection of PBDEs including BDE 209 that "[d]espite the heavy use of mass spectrometry for the analysis of these compounds, it is ironic that few systematic studies of the full mass spectra of these compounds have

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[55] Jhong, Y.J. and Ding, W.H. Letter to the Editor: Method optimization for quantitation of decabromodiphenyl ether in sediments and earthworms using liquid chromatography/atmospheric pressure photoionization tandem mass spectrometry. *Rapid Commun. Mass Spectrom.* **2007,** 21:4158-4161.

[56] de Boer and Wells. Pitfalls in the analysis of brominated flame retardants in environmental, human and food samples – including results of three international interlaboratory studies. *Trends Analyt. Chem.* **2006,** 25(4):364-372.

[57] Takahashi *et al.* An intercalibration study on organobromine compounds: Results on polybrominated diphenylethers and related dioxin-like compounds. *Chemosphere* **2006,** 64:234-244.

[58] La Guardia *et al.* Detailed polybrominated diphenyl ether (PBDE) congener composition of the widely used penta-, octa-, and deca-PBDE technical flame-retardant mixtures. *Environ. Sci. Technol.* **2006**, 40, 6247-6254.

[59] Stapleton *et al.* In vivo and in vitro debromination of decabromodiphenyl ether (BDE 209) by juvenile rainbow trout and common carp. *Environ. Sci. Technol.* **2006,** 40(15):4653-8.

[60] Binelli *et al.* Improvements in the analysis of decabromodiphenyl ether using on-column injection and electron-capture detection. *J. Chromatogr. A.* **2006,** 1136:243-247.

[61] Eljarrat and Barcelo. Sample handling and analysis of brominated flame retardants in soil and sludge samples. *Trends Analyt. Chem.* **2004**, 23(10-11): 727-736.

[62] Björklund *et al.* Influence of the injection technique and the column system on gas chromatographic determination of polybrominated diphenyl ethers. *J. Chromatogr. A.* **2004**, 1041:201-210.

[63] Covaci *et al.* Determination of brominated flame retardants, with emphasis on polybrominated diphenyl ethers (PBDEs) in environmental and human samples – a review. *Environ. Int.* **2003,** 29:735-756.

[64] Kolic et al. (2008). The analysis of halogenated flame retardants by GC-HRMS in environmental samples. J Chrom Sci 47:83-91.

[65] Hites R. (2008) Electron impact and electron capture negative ionization mass spectra of polybrominated diphenyl ethers and methoxylated polybrominated diphenyl ethers. Envion Sci Technol 42::2243-2252.

appeared" and "incomplete mass spectra (usually the low mass ions are omitted), spectra with no interpretation, ions at the wrong mass numbers, tables with just a few ion abundances, or ECNI spectra taken without attention to the ion source temperature."

La Guardia et al. (2006) (page 6247) recounts that as late as 2000 satisfactory agreement between 18 laboratories for 14 different PBDEs in a series of standards, biological, and sediment samples was only achieved for BDE 47, and that "Results were inconsistent for the other commonly detected PBDE contaminants, most notably BDE-209." Although results from later studies (July 2005) improved, La Guardia et al. said "laboratories still experience difficulty in analyzing BDE-209 in biota and sediments", and "results for the other PBDEs tested diverged as analytes approached their detection limits".

The difficulty inherent in the analysis of BDE209 was highlighted by the 2003-2004 Centers for Disease Control NHANES survey of over 2,000 Americans (Sjodin *et al.* 2008). A special clean laboratory with strict quality control was needed; yet, the CDC was unable to measure DecaBDE in human serum (Sjodin et al. 2008). As of 2010, CDC has been unable to analyze DecaBDE in human milk (Daniels et al. 2010).

In general, the best results are obtained using a ^{13}C-internal standard, high resolution mass spectrometry with monitoring for molecular ions (e.g. not simple monitoring for Br- atoms or pentabromophenoxy ions) coupled with retention time, and frequent blank determinations.

Ecological Biomonitoring. This section should recognize the difficulty of DecaBDE analysis at trace levels in environmental matrixes, the low systemic bioavailability of DecaBDE observed in laboratory studies, and indicate that DfE has not assessed the suitability or accuracy of the analytical methods used in reports of DecaBDE's environmental detection.

Human Biomonitoring. The reference to DecaBDE's detection in breast milk should be deleted, and substituted with the information from Daniels et al. (2010) that the CDC was unable to analyze breast milk for DecaBDE. The statement that NHANES did not include DecaBDE in the US biomonitoring report should include that CDC was unable to analyze human serum for DecaBDE despite use of clean room specially constructed for analysis of PBDEs (Sjodin et al. 2008). The DfE document should include Sjodin et al.'s estimate of DecaBDE serum levels of 2 ng/g lipid weight.

List of Appendixes

1. Kociba et al. 1975. Results of a two-year dietary feeding study with decabromodiphenyl oxide (DBDPO) in rats. Journal of Combustion Toxicology 2:268-285.

2. Stenzel and Nixon. 1997. Decabromodiphenyl oxide (DBDPO): Determination of the vapor pressure using a spinning rotor gauge. Wildlife International, Ltd. Easton, MD.

3. Stenzel and Markley. 1997. Decabromodiphenyl oxide (DBDPO): Determination of the water solubility. Wildlife International, Ltd. Easton, MD.

4. MacGregor and Nixon. 1997. Decabromodiphenyl oxide: Determination of n-octanol/water partition coefficient. Wildlife International, Ltd. Easton, MD.

5. Swartz et al. 1975. Results of a reproduction study in rats maintained in diets containing decabromodiphenyl oxide. Toxicology Research Laboratory. Dow Chemical U.S.A.

6. Norris et al. 1973. Toxicological and environmental factors involved in the selection of decabromodiphenyl oxide as a fire retardant chemical. Applied Polymer Symposium No. 22: 195-219.

7. Aufderheide et al. 2001. Effect of decabromodiphenyl oxide on the survival and reproduction of the earthworm, Eisenia fetida. ABC Laboratories, Inc., Columbia, MI and Wildlife International, Ltd, Easton, MD.

8. Porch and Krueger. 2001. Decabromodiphenyl oxide (DBDPO): A toxicity test to determine the effects of the test substance on seedling emergence of six species of plants. Wildlife International, Ltd., Easton, MD.

9. Schaefer and Siddiqui. 2001. Decabromodiphenyl oxide (DBDPO): An activated sludge, respiration inhibition test. Wildlife International, Ltd., Easton, MD.

10. Schaefer and Flaggs. Potential for biotransformation of radiolabeled decabromodiphenyl oxide (DBDPO) in anaerobic sludge. Wildlife International, Ltd. Easton, MD.

11. BCFWin-DD_Source_Oct2008 error with correction.

12. 1977 MITI fish bioconcentration test summary.

Albemarle

Comment: Comments on the DRAFT of July 2012 Design for Environment Screening Level Hazard Assessment of Decabromodiphenyl Ethane (DBDPEthane); CASRN 84852-53-9

The materials referenced in the "List of Appendices" are available upon request by contacting Emma Lavoie at lavoie.emma@epa.gov or 202-564-0951. The study by Black, S. (2012) is *not* available upon request because it was claimed confidential.

COMMENTS

DRAFT of July 2012
Design for the Environment Screening Level Hazard Assessment of Decabromodiphenyl Ethane (DBDPEthane); CASRN 84852-53-9

Page 4.249. Metabolites, Degradants and Transformation Products. Lower brominated congeners have not been detected as metabolites in rat studies or degradants/ transformation products in aerobic/anaerobic bacterial studies.

Page 4.249. Analog. DfE utilizes decabromodiphenyl ether (DecaBDE) as a structural analog for DBDPEthane (Figure 1). The two substances share similarities, e.g. two aromatic rings, 10 bromine atoms, high molecular weight, large molecular size, limited solubility in water and organic solvents, and poor suitability to gas chromatography.

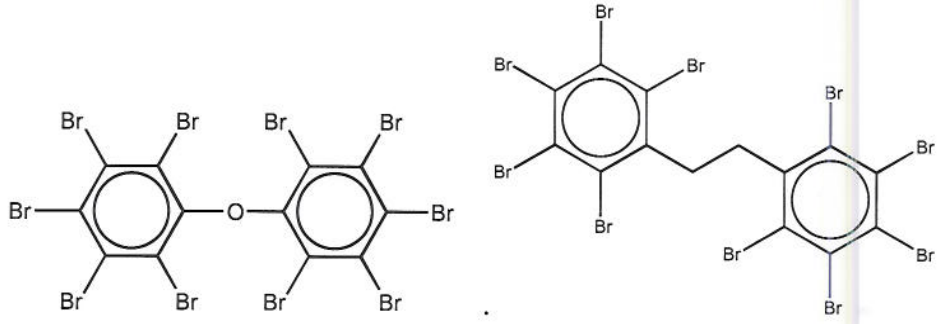

Figure 1. Structures of decabromodiphenyl ether (l) and decabromodiphenyl ethane (r).

The two molecules also have important differences (Table 1, Fig 2). DecaBDE exists as

Table 1. Comparison of molecular dimensions of DBDPEthane and DecaBDE.

Property	DecaBDPEthane		DecaBDE
	Most Stable	Least Stable	
Smallest enclosing sphere diameter (Å)	14.41	16.82	15.06
Smallest enclosing cylinder dimension (Å)	10.3	9.5	10.0
Spartan Surface area (Å^2)	408	417	390
Spartan Volume (Å^3)	400	400	372

*Dimensions were calculated as described in Louwen and Stedeford. 2011[1], and performed September 2012. Surface area and volume were calculated using Spartan based on the quantum mechanic calculated structures.

[1] Louwen and Stedeford. 2011. Toxicology Mechanisms and Methods 21(3):183-192.

one conformer due to bulky bromine atoms arranged around rings separated by a single oxygen. This constrains the molecule to one shape, e.g. the aromatic rings are arranged in space orthogonal to one another with an approximate 120° bend at the oxygen bridge. In contrast, DBDPEthane also has ten bromine atoms arranged around aromatic rings, but those rings are separated by a ethane bridge. The ethane bridge allows the molecule to assume different shapes. The most stable conformer is folded at the ethane bridge at an acute angle. Further, DBDPEthane has a larger molecular volume than DecaBDE. These differences in molecular shape will affect each molecule's behavior.

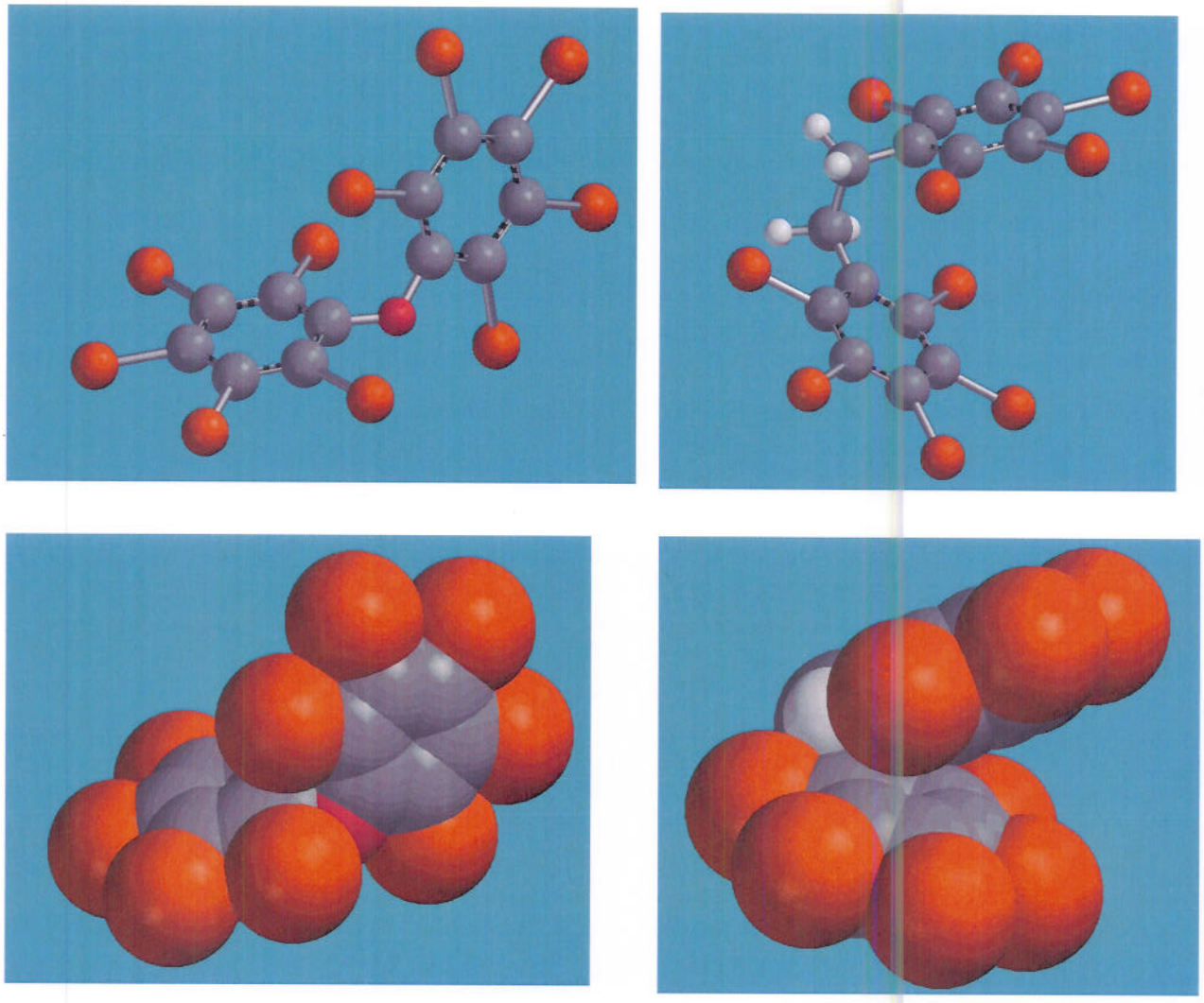

Figure 2. Structures of decabromodiphenyl ether (l) and decabromodiphenyl ethane(r).

Page 4.250. Low Kow. DBDPEthane's measured Log Kow is 3.55.[2] A copy of the final report from this guideline/GLP-compliant study is being submitted to DfE. Please correct the reference.

DfE should take into consideration DBDPEthane's limited solubility in water and octanol. When a substance has a low solubility in water *and* octanol, the resulting ratio could range from very low to very high, with no clear idea on how this would affect the magnitude of other properties, including BCF/BAF.[3]

DfE included comments derived from the UK's assessment of DBDPEthane. Page 7 of the UK's assessment says with respect to the measured Kow:

> A K_{ow} value has been measured for commercial EBP at 25°C using a column elution method (OPPTS 830.7560) in accordance with GLP (Van Hoven *et al*, 1999b). A copy of the study report was provided for this review. A generator column was prepared by loading an inert support material with ten millilitres of a saturated solution of the substance in n-octanol (which was prepared by mixing and sonication for 10 minutes, followed by centrifugation of the supernatant, then a final filtration through a 0.2 micron filter). Aqueous solutions of the test compound were produced by pumping water through the generator column. The aqueous solution leaving the column represented the equilibrium concentration of the test chemical that had partitioned from the n-octanol phase into the water phase. A log K_{ow} value of 3.55 was estimated by dividing the concentration of the substance in the n-octanol stock solution by the concentration measured in n-octanol-saturated water samples eluted from the column. This latter concentration (0.544 µg/L) was the mean of three measurements, all of which were below the limit of quantitation of 0.8 µg/L and above the limit of detection of 0.415 µg/L). Given this analytical uncertainty, the K_{ow} value was reported as an estimate.
>
> This test method is reportedly suitable for substances that have very low solubility in both water and organic solvents; it has been used in the same laboratory to determine the K_{ow} values for several other important brominated flame retardants including decaBDE (Albemarle, personal communication). The Environment Agency agrees that the method was suitable in principle, but considers the result to be unreliable for a substance that contains many bromine atoms. Given that the concentration in the water phase was very close to the measured water solubility (i.e. at or close to saturation), a higher stock solution concentration could have led to a higher K_{ow} value using this technique.[7]

The Log Kow measurement was conducted according to OPPTS 830.7560. The guideline states that the column's solid support is coated with an approximately 1.0 percent (w/w) solution of the compound in octanol. The UK was correct when saying that a *saturated* solution of DBDPEthane in octanol was used to load the generator column support material; DBDPEthane's solubility is limited, and concentrations higher than saturated are not possible. Further, a higher concentration in the octanol stock solution would not result in a higher Log Kow. This is because the method relies on the movement of the test substance from the octanol on the solid support into the aqueous phase. That movement is governed by the substance's water solubility; not by it's absolute concentration on the solid support.

DfE's comment, e.g. the measured Log Kow value is considered unreliable based on comparison to other substances with multiple bromine atoms, was taken from the UK assessment. Additional information on the UK's comment is available. The UK

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[2] Van Hoven et al. 1999. Saytex 8010: Determination of the n-octanol/water partition coefficient by the generator column method. Wildlife International, LtD. Easton, MD. APPENDIX 1.

[3] Sjim et al. 2007. Chapter 3. Transport, accumulation and transformation processes. In: Risk Assessment of Chemicals: An Introduction, pg 73-158. Eds: C.J. van Leeuwen and T.G. Vermeire. Springer.

conducted a peer review regarding possible conduct of another Kow study after the assessment's conclusion. Albemarle Corporation was given the opportunity to respond to the peer review.[4] Our response raised a number of issues. What we 'know' about log Kow values for polybrominated substances was especially questioned. The impact of DBDPEthane's insolubility in water and octanol on the partition coefficient measurement was discussed. The need for another measurement, in light of the mammalian/ecotoxicity data in existence and under generation, was discussed. The UK has not continued a quest for a more 'reliable' Kow measurement.

The comments in the DfE document regarding DBDPEthane's measured Log Kow value should be deleted.

Page 4-251. Human Health Effects. Toxicokinetics. Summary. We agree that DBDPEthane is unlikely to be absorbed dermally whether as the neat material or in solution. We agree DBDPEthane is poorly absorbed from the gastrointestinal tract and is expected to be poorly absorbed from the lungs. Elimination in the feces is the route of excretion.

DfE states "If absorption does occur, decabromodiphenyl ethane is distributed to the serum, liver, kidney and adipose tissues and undergoes biotransformation to form metabolites." This comment was based on Wang et al. (2010)[5] and should be deleted for the following reasons.

1). Two pharmacokinetic studies in the rat using ^{14}C-DBDPEthane have been unable to detect ^{14}C-activity in amounts higher than background in blood, plasma or tissues.

2.) Wang et al. did not analyze serum for DBDPEthane or metabolites. Serum was solely used for clinical chemistries and thyroid hormone analyses.

3). Wang et al. administered a cumulative 90-d dose of DBDPEthane of ~3000 mg. The sum of DBDPEthane reported in liver, adipose and kidney was ~0.000005% of the cumulative dose. Commenting that DBDPEthane is distributed to these organs based on the negligible amounts reported is misleading.

The portion of the cumulative dose detected in liver, kidney and adipose was estimated as follows. Based on the rats' mean weight at the end of the study (Table S3, Wang et al. 2010) and estimated weight at study initiation, the rats received roughly 3000 mg DBDPEthane over 90-days. The percent of the total dose in liver at day 90 can be estimated assuming a liver lipid content of 5%, the liver weight in Table S2, and the

[4] Hardy M. 2006. Response To Reveiwers' Comments On The UK's June 2006 Draft For Peer Review Environmental Risk Evaluation Report: 1,1'-(Ethane-1,2-diyl)bis[penta-bromobenzene] (CAS no. 84852-53-9). APPENDIX 2.

[5] Wang et al. 2010. Comparative tissue distribution, biotransformation and associated biological effects by decabromodiphenyl ethane and decabrominated diphenyl ether in male rats after a 90-day oral exposure study. Environ Sci Techn 44:5655-60.

reported EBP liver content of ca. 200 ng/g lipid. Using these values, the liver contained ca. 140 ng EBP or ca. 0.0000047 % of the total dose. Similar calculations indicate ca. 0.000001 % of the total dose was detected in adipose (assuming a total body adipose content of 15% of body weight, 80% fat content of adipose, 550 ng/g lipid in adipose). The kidney content was so low as to be insignificant in comparison to liver and adipose, and not included in these calculations.

4). Wang et al.'s analytical method was nonspecific. Whether DBDPEthane was actually detected in liver, adipose or kidney is questionable. Co-authors of Wang et al. incorrectly reported detection of DBDPEthane in panda testicles.[6] Wang et al.'s analytical method was that in the panda paper, e.g. Hu et al. 2008.[7] Similar to the Hu et al. 2008 publication, the Wang et al. 2010 publication has serious deficiencies and has been criticized in the literature.[8]

5.) The identity of a purported metabolite as 'methyl sulfone' derivative is questionable. The mass spectra of presumed metabolites do not coincide with that expected for the proposed structures (Banasik et al. (2011)):

> Fourth, it is unclear how the authors deduced a molecule with a methyl- or ethyl-sulfone group substituted on the ring. Based on computer modeling software, the proposed structures do not have the correct bromine isotopic pattern as shown in Wang et al.'s Figures 3 and S3,[1] and the authors are identifying fragmentation patterns that are below the S/N in the given figures. In Wang et al.'s Figure 3 and S2[1] the fragmentation patterns of the two molecules are inconsistent with molecules of similar structure, with the "methyl-sulfone" moiety having a strong M-2Br and the "ethyl-sulfone" moiety showing a stronger parent and weak M-2Br; in addition, there is no indication of m/z = 160/162 for the "ethyl-sulfone" molecule as the authors state on page 5657. Also, the differences in relative retention times for peaks 3 and 7 are not consistent with a single methyl group difference. Any proposed structures from a complete unknown impurity or metabolite should have accurate mass measurements to support their inference and an extended mass range to ensure the parent molecule is detected. The authors assumed ". . .the relative response factors for the three unknown metabolites were similar. . ." to known compounds, but without known structures and authentic standards, response factors cannot be predicted.[1]

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[6] Hardy and Ranken 2008. Comment on "Brominated flame retardants, polychlorinated biphenyls, and organochlorine pesticides in captive Giant Panda (Ailuropaoda melanoleuca) and Red Panda (Ailurus fulgens) from China. Environ Sci Technol 42: 8172-8172.

[7] Hu et al. 2008. Brominated flame retardants, polychlorinated biphenyls, and organochlorine pesticides in captive Giant Panda (Ailuropaoda melanoleuca) and Red Panda (Ailurus fulgens) from China. Environ Sci Technol 42:4704-4709.

[8] Banasik et al. 2011 Comment on "Comparative tissue distribution, biotransformation and associated biological effects by decabromodiphenyl ethane and decabrominated diphenyl ether in male rats after a 90-day oral exposure. Environ Sci Technol 45:5000-5001.

6.) Metabolite formation and identity is immaterial given the absence of toxicity at the administered, as well as higher, doses. Nevertheless, the unknowns reported as 'metabolites'are not known to be derived from the test material. Identification as metabolites of the test substance would require labeled test material and subsequent analysis of peak(s) containing the label. Wang et al did not use a labeled test material.

7.) McKinney et al. (2011)[9] reported *in vitro* hepatic microsomal preparations from polar bear, beluga whale, ringed seal, and rat did not metabolize DBDPEthane.[10]

The comment in the Summary that if absorbed DBDPEthane is distributed and undergoes biotransformation should be deleted.

Page 4-251. ADME. Oral, Dermal, or Inhaled. Reference: Wang et al. 2010. Please correct the data section of the Wang et al. study.

DfE's data quality section on Wang et al. mentions radioactivity. Wang et al. did not use radiolabeled test material. Radiolabeled test material was used in the study cited as "Hardy, 2004".

Page 4-251. ADME. Oral, Dermal, or Inhaled. Please add the recently completed ADME study using ^{14}C-DBDPEthane.[11]

> Blood, tissues, urine and feces were collected at various time points from rats administered a single oral dose of labeled and unlabelled DBDPEthane. Groups of noncatheterized, bile duct- and jugular vein-catherized rats were included in the study. Nearly all of the ^{14}C-activity (~90%) was recovered in the feces and suggests DBDPEthane is excreted quantitatively in the feces. Only background levels of ^{14}C-activity were detected in bile, blood, urine or plasma at all time points. Compounds with molecular weights >300 are generally eliminated in the bile and feces, and the absence of ^{14}C-activity in the bile indicates DBDPEthane is not taken up from the GI tract into the enterohepatic circulation. The lack of radioactivity in blood and plasma indicates DBDPEthane has negligible systemic bioavailability. Tissues analyzed were spleen, liver, kidney, adipose, stomach plus contents, small intestine plus contents, cecum plus contents, and large intestine plus contents. Only background levels of ^{14}C-activity were detected in spleen, liver, kidney and adipose tissue. ^{14}C-activity above background was detected with the analysis of the combined intestinal-contents-plus-intestinal- tract-organs. The ^{14}C-activity moved distally in the GI tract with time post-doing. Pooled fecal extracts (0-24 h, 24-48 h) were analyzed via HPLC-UV/ßRAM. Feces collected at 0-24 post dosing contained ~70% of the administered dose, while that collected 24-48 h post-dosing contained ~20% of the

[9] McKinney et al. 2011. Comparative hepatic microsomal biotransformation of selected PBDEs, including decabromodiphenyl ether, and decabromodiphenyl ethane flame retardants in artic marine-feeding mammals. Envion Toxicol Chem 30:1506-1514.

[10] Hardy M. 2012. Unrecognized causative factors for the lack of in vitro metabolism reported by McKinney et al. Environ Toxicol Chem 31:1184-1186.

[11] Black S. 2012. Pharmacokinetic studies of [14C]Decabromodiphenyl ethane (EBP). RTI/0212983.001.002. RTI International, Research Triangle Park, NC. APPENDIX 3.

dose. The majority of the radioactivity at either collection period eluted at the retention time of the parent molecule. An additional, small peak containing the radiolabel eluted prior to the parent molecule. The data indicate DBDPEthane is not absorbed from the GI tract. This is supported by the high recovery in feces coupled with essentially background radioactivity levels in urine, bile, blood, plasma and tissues. HPLC-UV/ßRAM analysis of feces indicated DBDPEthane was excreted unchanged in the feces, without prior absorption, following oral administration.

Page 4-252. Carcinogenicity. Summary. DfE rates DBDPEthane as MODERATE based on analogy to decabromodiphenyl ether (DecaBDE), professional judgment, and potential for bioaccumulation.

DfE correctly notes in the DATA column that experimental carcinogenicity data is not available on DBDPEthane. The results described in this column relate to NTP's 2-year studies in rats and mice of DecaBDE.[12] NTP reported some, equivocal and no evidence of carcinogenicty in rats, male mice and female mice, respectively. Doses were up to 2,550 mg/kg/d in rats and 7,780 mg/kg/d in mice. NTP also reported a lack of mutagenicity/carcinogenicity in multiple studies on DecaBDE.

In assigning a carcinogenicity rating, DfE did not consider another two-year study in rats that found no evidence of carcinogenicity or toxicity in rats fed DecaBDE at doses substantially lower than those used by NTP, e.g. Kociba et al. 1975.[13] These results are critically important because

a) When tested at lower doses, no carcinogenicity (or toxicity) was observed in the species (rat) with the highest, e.g. "some" [14], evidence in NTP's study,

b) The effects observed in the NTP two-year study are threshold-related,

c) The highest dose fed in the Kociba et al. study was within the range where first order absorption kinetics would be expected[15], whereas zero order absorption kinetics would be expected at the doses fed by NTP,

d) DfE assigns a LOW hazard for substances with "Negative studies or robust mechanism-based SAR".

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[12] NTP 1986. Toxicology and Carcinogenesis Studies of Decabromodiphenyl Oxide (CAS No. 1163-19-5) in F344/N Rats and B6C3F1 Mice (Feed Studies). Research Triangle Park, NC. National Toxicology Program Technical Report Series No. 309.

[13] Kociba et al. 1975. Results of a two-year dietary feeding study with decabromodiphenyl oxide (DBDPO) in rats. Journal of Combustion Toxicology 2:268-285.

[14] NTP describes its results as clear, some, equivocal and no evidence of carcinogenicity for species and gender. Some evidence of carcinogenicity was reported in male and female rats due to hepatic neoplastic nodules. Equivocal evidence was reported in male mice, and was influenced by the number of early deaths in the control group. No evidence was found in female mice. Thus, the highest evidence in the NTP study was reported in rats.

[15] Biesemeier et al. 2010. Effects of dose, administration route, and/or vehicle on decabromodiphenyl ether concentrations in plasma of maternal, fetal, and neonatal rats and in milk of maternal rats. Drug Metab Dispo 38(10):1648-1654.

DfE did not take these points into consideration when deriving a MODERATE rating for DecaBDE, and by analogy, DBDPEthane. A LOW hazard is appropriate for both substances.

Irrespective of the above, the manner in which DfE assigns a MODERATE is highly questionable. A MODERATE hazard is assigned to any substance with "limited or marginal evidence of carcinogenicity in animals (and inadequate evidence in humans)". DfE does not explain how limited or marginal evidence of carcinogenicity translates into a MODERATE human health hazard beyond stating "When limited or marginal data on carcinogenicity are present, a designation of MODERATE will be used."[16] Potency, genotoxicity/mutagenicity and other key factors are not considered. This is in direct contradiction to EPA's Guidelines for Carcinogen Risk Assessment[17] that clearly state these and other key data are to be considered during hazard assessment. DfE's manner in which a MODERATE rating is assigned is in conflict with Agency guidelines. DfE's rating system is inherently biased and misleading.

DfE asserts (pg 12) that its criteria mirror the classification approach used by IARC. However, IARC does not *rate* hazard. IARC *classifies* substances according to the strength of the evidence. IARC classifies DecaBDE in Group 3, not classifiable as to its carcinogenicity to humans.

IARC Group 3 is defined as:

> Group 3: The agent is *not classifiable as to its carcinogenicity to humans.*[18]
>
> This category is used most commonly for agents for which the evidence of carcinogenicity is *inadequate* in humans and *inadequate* or *limited* in experimental animals.
>
> Exceptionally, agents for which the evidence of carcinogenicity is *inadequate* in humans but *sufficient* in experimental animals may be placed in this category when there is strong evidence that the mechanism of carcinogenicity in experimental animals does not operate in humans.
>
> Agents that do not fall into any other group are also placed in this category.
>
> An evaluation in Group 3 is not a determination of non-carcinogenicity or overall safety. It often means that further research is needed, especially when exposures are widespread or the cancer data are consistent with differing interpretations.

The Hazardous Substances Database reports IARC's finding with respect to DecaBDE[19] as:

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[16] US EPA. Design for the Environment Program Alternatives Assessment Criteria for Hazard Evaluation. Version 2.0. August 2011. Office of Pollution Prevention & Toxics. Environmental Protection Agency. Pg 12.

[17] US EPA 2005. Guidelines for Carcinogen Risk Assessment. EPA/630/P-03/001F. Risk Assessment Forum. U.S. Environmental Protection Agency, Washington, DC.

[18] http://monographs.iarc.fr/ENG/Preamble/currentb6evalrationale0706.php.

[19] http://toxnet.nlm.nih.gov/cgi-bin/sis/search/a?dbs+hsdb:@term+@DOCNO+2911

Evidence for Carcinogenicity:
Evaluation: No epidemiological data relevant to the carcinogenicity of decabromodiphenyl oxide. There is limited evidence in experimental animals for the carcinogenicity of decabromodiphenyl oxide. Overall evaluation: decabromodiphenyl oxide is not classifiable as to its carcinogenicity to humans (Group 3). [IARC. Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Geneva: World Health Organization, International Agency for Research on Cancer, 1972-PRESENT. (Multivolume work). Available at: http://monographs.iarc.fr/index.php p. V71 1368 (1999)] **PEER REVIEWED**

Page 4-254. Neurotoxicity. DfE rates DBDPEthane as HIGH based on analogy to DecaBDE and professional judgment. The rating was based on a study published in the literature that DfE indicated was a screening study. No further information was given.

DfE's description of the screening study indicates the Viberg study in neonatal mice, used by IRIS in 2008 to set DecaBDE's RfD of 0.007 mg/kg/d. That study has been superceded by a robust guideline/GLP-compliant developmental neurotoxicity study on DecaBDE.[20] The NOAEL in the guideline study was 1000 mg/kg/d administered to maternal rats over gestation and lactation. We also note that the experimental design used in the Viberg studies has been found unacceptable by authors affiliated with EPA[21], whereas authors affiliated with EPA concluded studies performed according to the developmental neurotoxicity guideline represent the best science for assessing the potential for such effects.[22] A peer-reviewed publication reported that IRIS wrongly relied on the Viberg study in developing an RfD.[23] A second peer-reviewed publication compared results from studies performed using the Viberg experimental design and determined a lack of consistency precluded a causal relationship.[24]

Further details are provided in our comments on DecaBDE.

DfE's reliance on the Viberg study is not justified. The guideline/GLP-compliant DNT study demonstrates DecaBDE is not a developmental neurotoxicant. DecaBDE, and DBDPEthane, should both be rated LOW for this endpoint.

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[20] Biesemeier et al. 2011. An oral developmental neurotoxicity study of decabromodiphenyl ether (DecaBDE) in rats. Birth Defects Res Part B 92:17-35.
[21] Holson et al. 2008. Statistical issues and techniques appropriate for developmental neurotoxicty testing: a report from the ILSI Research Foundation/Risk Science Institute expert working group on neurodevelopmental endpoint. Neurotoxicol Teratol 30:326-348.
[22] Makris et al. 2009. A retrospective performance assessment of the development neurotoxicity study in support of OECD test guideline 426. Environ Health Perspect 117:17-25.
[23] Goodman J 2009. Neurodevelopmental effects of decabromodiphenyl ether (BDE 209) and implications for the reference dose. Regul Toxicol Pharmacol 54:91-104.
[24] Williams and DeSesso. 2010. The potential of selected brominated flame retardants to affect neurological development. J Toxicol Environ Health, Part B 13:411-448.

Page 4-255. Repeated Dose Effects. Summary. DfE correctly rates DBDPEthane as LOW for repeated dose effects based on 28-d and 90-d studies in rats. A NOAEL of ≥ 1000 mg/kg/d, the highest dose tested, is correctly assigned to the rat 28-d study. The highest dose tested in the 90-d study, 1000 mg/kg/d, is incorrectly said to be a low-adverse-effect-level (LOAEL). The effects reported were clearly not adverse, and DfE's interpretation is erroneous.

DfE also compares DBDPEthane to decabromodiphenyl ether, and therefore assumes potential for bioaccumulation, and states "there is potential for expression of adverse effects in long term studies". This interpretation is also erroneous.

90-Day Study NOAEL. DfE interpreted the hepatic findings at 1000 mg/kg/d in the DBDPEthane 90-day study, e.g. increased liver weight, minimal to slight hepatocellular vacuolation and minimal to slight centrilobular hepatocytomegaly in male rats, to be adverse. DfE then identified the 1000 mg/kg/d dose as a LOAEL based on a conservative approach.

DfE's decision is not based on sound science. DfE must differentiate between *observed* versus adverse effects. The minimal to slight centrilobular hepatocytomegaly and vacuolation in male rats do not reflect adverse changes. Such changes are commonly observed after prolonged administration of substances eliminated by the liver, and are representative of an adaptive, not adverse, change. Centrilobular hepatocyte hypertrophy is a common adaptive response of rodent liver to a large number of xenobiotics.[25],[26],[27] The liver hypertrophy merely reflects a physiological response to increased demand on the tissue for increased function[28], and is not considered a toxic response.[29]

Importantly, the liver changes in male rats had resolved without any delayed or long-term toxic effects following a 28-d recovery period, clinical chemistry parameters did not indicate evidence of hepatotoxicity, and no treatment-related changes were found in female rats.

In deciding the liver changes were adverse, DfE over-rules conclusions reached in

- the final report of the 90-d study,
- the peer-reviewed publication of the 90-d study,[30]

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[25] Greaves P 2000. Liver in Handbook of Preclinical Toxicity Studies: Interpretation and relevance in drug safety evaluation. p404. Elsevier, Amsterdam.

[26] McGuire et al. 1986. Evaluation of chronic toxicity and carcinogenesis in rodents with synthetic analgesic tilidine furamate. Toxicology 39, 149-163

[27] Williams GM and Iatropoulos MJ 2002. Alteration of liver cell function and proliferation: Differentiation between adaptation and toxicity. Toxicologic Pathology 30, 41-53.

[28] Wallig MA 2000. Morphologic manifestation of toxic cell injury in Handbook of Toxicologic Pathology Vol 2, 2nd Edition, Eds Haschek WM, Rousseaux CG and Wallig MA, p41, Academic Press, New York.

[29] Cattley RC and Popp JA 2000. Liver in Handbook of Toxicologic Pathology Vol 2, 2nd Edition, Eds Haschek WM, Rousseaux CG and Wallig MA p202, Academic Press New York

[30] Hardy et al. 2002. The subchronic oral toxicity of Ethane, 1,2-Bis(pentabromophenyl) Saytex 8010) in rats. Internat J Toxicol 21:165-170.

- the UK's risk assessment of DBDPEthane[31], and

- an independent review of the liver slides conducted for the UK risk assessment by an experienced pathologist, C. Gopinath, BVSc; MVSc; PhD, FRCPath.

The NOAEL for DBDPEthane in this 90-d is ≥ 1000 mg/kg/d, the highest dose tested, and DfE's screening level hazard assessment should reflect this.

Potential for expression of adverse effects in long term studies. DfE expresses concern for DBDPEthane based on the minimal histopathologic changes observed in NTP's two-year studies in rats and mice fed DecaBDE at uncommonly high doses. Dietary doses in the NTP two-year study were:

- Male rats: 0, 1,120, and 2,240 mg/kg/d,
- Female rats: 0, 1,120, and 2,550 mg/kg/d,
- Male mice: 0, 3,200, and 6,650 mg/kg/d,
- Female mice: 0, 3,760, and 7,780 mg/kg/d.

The histopathologic changes observed in rats in the DecaBDE 2-year study were:

- Male rats: 2,240 mg/kg/d: hepatic thrombosis and degeneration, spleenic fibrosis, lyphoid hyperplasia of mandibular lymph node
- Male rats: 1,120, 2,240 mg/kg/d: slight increase in acanthosis of forestomach
- Female rats: 1,120, 2,240 mg/kg/d: slight increase in spleenic fibrosis.

This study is remarkable for the minimal histologic changes observed in either rats or mice, especially when the dietary doses are considered. Rats consumed 1.1 to 2.5 times the limit dose of 1000 mg/kg/d over the course of the study. Mice consumed 3.2 to 7.7 times the limit dose. DfE must take this into consideration when expressing concern for potential adverse effects after chronic exposures.

Forestomach acanthosis, e.g. thickening of the epithelium in the nonglandular portion of the stomach, is not relevant to human health assessment. An anatomical feature comparable to the rodent forestomach is not found in humans.[32] Thus, the change is not relevant to DecaBDE's assessment.

Hepatic thrombosis and degeneration, and spleenic fibrosis are changes commonly observed in F344 rats affected with mononuclear cell leukemia.[33], [34] The rats in the NTP

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[31] Dungey and Akintoye. 2007. Environmental risk evaluation report: 1,1'-(Ethane-1,2-diyl)bis[penta-bromobenzene]. CAS: 84852-53-9. SCHO0507BMOR-E-P. U.K. Environment Agency. Bristol, UK.
[32] Frantz et al. 1991. Proliferative lesions of the non-glandular and glandular stomach in rats. In: Guides for Toxologic Pathology. STP/ARP/AFIP, Washington, DC.
[33] Suttie A. Histopathology of the Spleen. Toxicl Path 34:466-503.2006.
[34] Stromber P and Vogtsberg P. 1983. Pathology of Mononuclear cell leukemia of Fischer rats. I. Morphologic Studies. Vet Pathol 20:698-708.

study were affected with mononuclear cell leukemia; at the time of the study, control male rats in the DecaBDE two year study had the highest incidence of leukemia ever reported in untreated controls in NTP feed studies. The hepatic and spleen changes are likely related to the leukemia, rather than DecaBDE.[35]

Lymph node hyperplasia is a normal response to antigens.[36] It is not an adverse effect. The increased incidence of hyperplasia in mandibular lymph nodes of high dose male rats was not observed at either dose in the 5 other lymph nodes evaluated: mediastinal, pancreatic, mesenteric, renal and iliac. Hyperplasia in 1 of 5 nodes in one dose only suggest an incidental, rather than treatment-related, change.

Histopathologic changes in mice were:

- Male mice, 3200 mg/kg/d: hepatic granulomas
- Male mice, 3200, 6650 mg/kg/d: hepatic centrilobular hypertrophy, thyroid follicular cell hyperplasia.

These histologic changes occurred at doses 3.2 and 6.6 times the limit dose of 1000 mg/kg/d, and are not relevant to human hazard evaluation. Further, the increased incidence of hepatic granulomas was not dose related. The increased incidence of hepatic centrilobular hypertrophy and thyroid follicular cell hyperplasia is again related to the extraordinary doses and likely related to a rodent-specific mechanism of action referable to an adaptive response of the liver.

A concern for adverse effects due to chronic exposure based on NTP's two-year study is not relevant to the human health assessment of DecaBDE.

Additionally, DfE did not consider that no adverse effects were observed in a two-year study in rats at substantially lower doses, e.g. Kociba et al. 1975. Therefore, low dietary doses, which are more representative of environmental exposures than the extraordinary doses fed in the NTP study, do not induce chronic toxicity.

The comment regarding potential for expression of adverse effects in long-term studies should be deleted.

Page 4-258. Fish LC50. Study attributed to Hardy 2004. Please correct the reference to Hardy et al. 2012.[37] Please correct the Data Quality section. OECD guidelines do not state that WAFs should only be used with multi-component substances. As noted in Hardy et al. (2012), the WAF methodology was utilized for acute studies in daphnia, fish and algae because:

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[35] Hardy et al. 2009. Toxicology and human health assessment of decabromodiphenyl ether. Critical Reviews in Toxicology 39(S3):1-44.

[36] Frith et al. 1996. Proliferative lesions of hematopoietic lymphatic systems in rats. In: Guides for Toxologic Pathology. STP/ARP/AFIP, Washington, DC.

[37] Hardy et al. 2012. Studies and evaluation of the potential toxicity of decabromodiphenyl ethane to five aquatic and sediment organisms. Ecotox Environ Saf 75:73-79.

> The tests would be performed at water concentrations equal to or below DBDP-Ethane's measured water solubility. However, DBDP-Ethane is an extremely difficult substance with which to work, especially in the aquatic arena. It became apparent during analytical method development that DBDP-Ethane's negligible solubility in water and organic solvents, and the difficulty associated with generation and analysis of stable water concentrations precluded the traditional flow-through tests as well as valid analytical monitoring of test concentrations. As a result, all three acute aquatic tests were performed using the water accommodated fraction (WAF) without measurement of DBDP-Ethane water concentrations (Girling, 1989; Girling et al., 1992, 1994; OECD, 2004).

Page 429. Daphnia LC50. Study attributed to Hardy 2004. Please see the above comments relating to Fish LC50.

Page 429. Green Algae EC50. Study attributed to Hardy 2004. Please see the above comments relating to Fish LC50.

Page 4-261. Sediment Dwelling Organisms ChV. Please correct the reference to Hardy et al. 2012.

Page 4-261. Earthworm Subchronic Toxicity. Please correct the reference to Hardy et al. 2011.[38]

Page 4-264. Bioaccumulation. Summary. DfE assigns a HIGH concern to DBDPEthane based on monitoring data in aquatic and terrestrial species, while stating that experimental data in fish are below a level of concern. No information was provided on the monitoring data considered by DfE in reaching a conclusion of HIGH bioaccumulation.

BCF/BAF values. Page 4-23 of DfE's draft document indicates experimental BAF or BCF values can be compared directly to the DfE criteria to assign a hazard designation. The experimental BAF/BCF < 100 is designated LOW. Two experimental BCF values for DBDPEthane are available, and both are < 100. Page 4-23 further says, if experimental BCFs < 100 are available, the estimated upper trophic BAF from EPISuite was used preferentially. While this latter statement is contrary to the DfE's program's assessment criteria[39], the estimated upper trophic BAF for DBDPEthane is 62, e.g. < 100. Thus, DfE draft document's own criteria translate into a LOW rating for DBDPEthane.

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[38] Hardy et al. 2011. Terrestrial toxicity evaluation of decabromodiphenyl ethane on organisms from three trophic levels. Ecotoxicol. Environ Saf 74:703-710.

[39] Design for the Environment Program Alternatives Assessment Criteria for Hazard Evaluation. V 2.0, August 2011. Office of Pollution Prevention & Toxics. U. S. Environmental Protection Agency.

Molecular size and shape. DBDPEthane's molecular size and shape are indicative of a low bioaccumulation potential (Table 1, Figures 1,2). Molecular properties influence bioaccumulation.

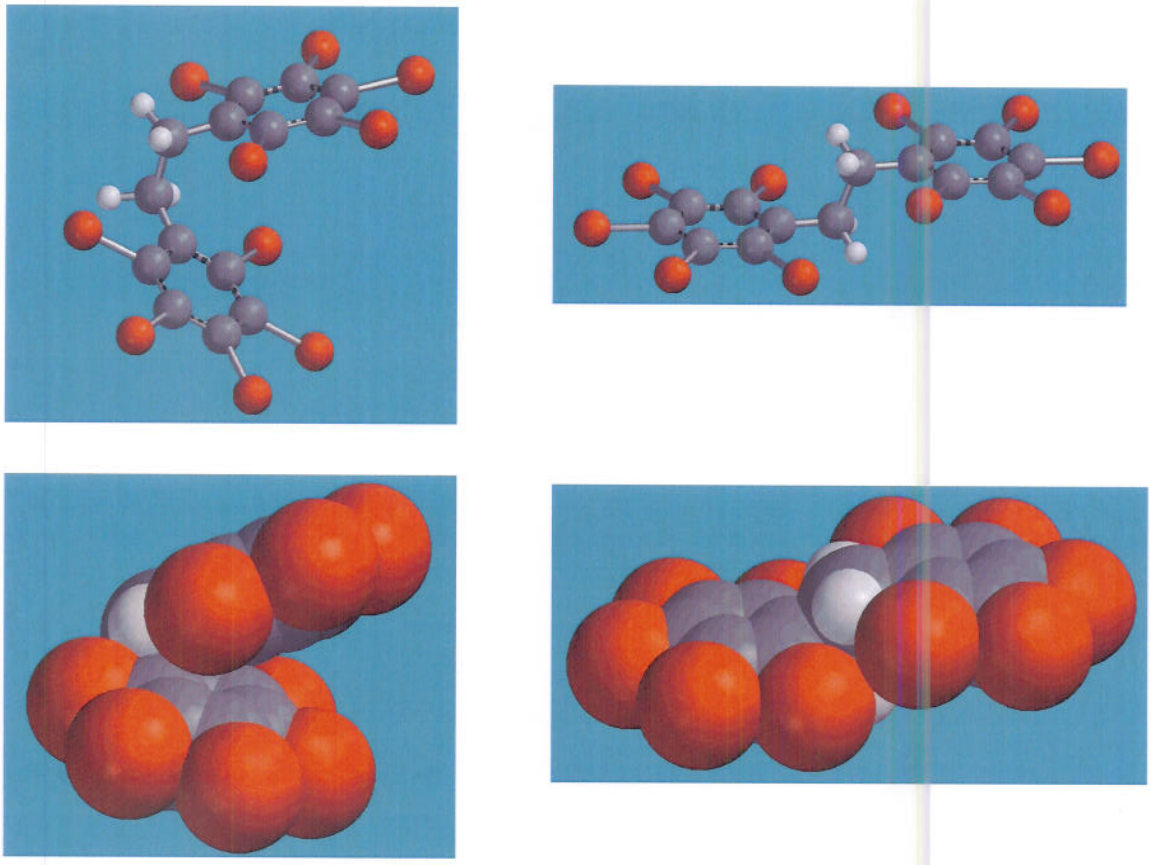

Figure 2. DBDPEthane' most (l) and least (r) stable conformers. Orange spheres represent bromine atoms, grey spheres carbon atoms, and white spheres hydrogen atoms.

A prerequisite for bioconcentration or bioaccumulation is absorption. Chemicals with molecular weights >600 are poorly absorbed by fish[40],[41],[42],[43] and a molecule weight of 1000 is generally used as the cut-off value for absorption when assessing mammalian

[40] Niimi and Oliver 1988. Influence of molecular weight and molecular volume on dietary absorption efficiency of chemicals by fishes. Can J Fish Aquat Sci. 45:223-227.
[41] Zitco 1974. Uptake of chlorinated paraffins and PCB from suspended solids and food by juvenile Atlantic salmon. Bull. Environ. Contam. Toxicol. 12:406-412
[42] Tulp and Hutzinger 1978. Some thoughts on aqueous solubilities and partition coefficients of PCB, and the mathematical correlation between bioaccumulation and physico-chemical properties. Chemosphere 10: 849-860.
[43] Bruggeman et al. 1984. Bioaccumulation of super-lipophilic chemicals in fish. Toxicol. Environ. Chem. 7: 173-189.

hazard. For example, absorption efficiency by fish from the diet for chemicals with molecular weight >650 ranged from 'nil' to 0.01 (Niimi and Oliver 1988). DBDPEthane's molecular weight, 971.2, is nearly 1000. With respect to brominated aromatic compounds, bioconcentration/accumulation is negatively correlated with the degree of bromination.[44],[45] Burreau et al. (2004) reported reduced bioconcentration (and no biomagnification) for high molecular weight polybrominated diphenyl ethers, with six or more bromines, molecular weights 644-959. Based on molecular weight alone, DBDPEthane would be predicted to be poorly absorbed, and thus exhibit low accumulation.

Molecular size can be expressed in several ways: cross-sectional diameter, total surface area, molecular volume, dimensional length, etc. Niimi and Oliver (1988) reported that chemicals with molecular volumes over 0.3 nm^3 (300 $Å^3$) are poorly absorbed. Substances with a cross-sectional diameter of >0.95 nm generally do not bioaccumulate due to limited membrane permeability[46], although there are notable exceptions. To account for the exceptions, Dimitrov et al. (2002)[47] refined the maximum molecular length to a threshold not exceeding 1.5 nm, e.g. the maximum tolerance of the cell membrane. For chemicals > 1.5 nm in length, uptake appeared via some mechanism other than passive diffusion. Conformation flexibility also appears important because flexibility can further decrease passage through the membrane and hence decrease uptake.

The DBDPEthane molecule has 16 different conformers with a number of different shapes. The actual molecule will vibrate through these conformers spending the most time in the more stable configurations (Table 1, Figure 1). The most stable conformer is more compact than one would expect based on a two-dimensional drawing of the molecule. However, even though more compact than expected, the size of the most stable EBP conformer is > 300 $Å^3$. Further, DBDPEthane's longest dimension of one of its stable conformers is greater than the critical 1.5 nm value (data not shown). Thus, DBDPEthane's molecular size is expected to limit its absorption by biological systems.

DBDPEthane's smaller than expected molecular size of its most stable conformer is due to the ethane linkage between the two aromatic rings, and resultant folding. This ethane bridge gives the molecule a good degree of flexibility, which also impacts the molecule's absorption. Flexibility tends to decrease absorption whereas rigidity assists passive diffusion through cell membranes (Dimitrov et al. 2002).

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[44] Hardy M. 2004. A comparison of the fish bioconcentration factors for brominated flame retardants with their nonbrominated analogues. Environ Toxicol Chem 23:656-661.

[45] Burreau et al. 2004. Biomagnification of polychlorinated biphenyls (PCBs) and polybrominated diphenyl ethers (PBDEs) studied in pike (*Esox lucius*), perch (*Perca fluviatilis*) and roach (*Rutilus rutilus*) from the Baltic Sea. Chemosphere 55:1043-1052.

[46] Sijm et al. 1993. Ethyl m-aminobenzoate methansulfonate dependent and carrier dependent pharmacokinetics of extremely lipophilic compounds in rainbow trout. Arch. Environ. Contam. Toxicol. 25:102-109.

[47] Dimitrov et al. (2002). Predicting bioconcentration factors of highly hydrophobic chemicals. Effects of molecular size. Pure Appl. Chem. 74 10: 1823-1830.

Solubility in octanol has been suggested as an indicator of bioaccumulation potential.[48] Substances that have an octanol solubility below 0.002 x molecular weight (<2 mg/L), are not expected to bioaccumulate. A very low solubility in octanol suggests that only low body burdens would build up in an aquatic organism. DBDPEthane's solubility in octanol has not been directly measured. A value of 1.91 mg/L was measured in the octanol/water partition coefficient study.

Thus, several of EBP molecular properties severely limit its diffusion through cell membranes. This limited diffusion is reflected in DBDPEthane's toxicology results (e.g. no bioconcentration in fish, limited or no uptake in rats, high NOEL in repeated dose studies).

It is improbable that tissues of wildlife contain DBDPEthane. In addition to the lack of accumulation noted in the laboratory fish study, ^{14}C-pharmacokinetic studies in rats indicate essentially no uptake (see section on ADME in these comments). Albemarle Corporation is investigating DBDPEthane's distribution to avian eggs, and the work-in-progress indicates non-detectable levels in eggs after repeated doses of up to 1000 mg/kg/d. Given DBDPEthane's properties, its difficult analysis, its poor absorption, and the nonspecific methods of analysis used in published reports of minute environmental levels, it is highly unlikely that DBDPEthane was actually detected in terrestrial and aquatic species in the environment.

DBDPEthane's potential for bioaccumulation is LOW.

Page 4-465. Environmental Monitoring and Biomonitoring. The environmental and ecological monitoring results reported by DfE are Kierkegaard 2004, Ricklund et al. 2010 and 2008, and Betts 2009. The Kierkegaard and Ricklund papers report extremely low levels (ng/g) in sewage sludge and sediment. The Ricklund papers used non-specific methods of analysis (MS with m/z=79, 81 for bromide ion).

Under Ecological Biomonitoring, DfE cites to Betts (2009) indicating detection in seagulls, Chinese water birds (in China), pandas (in China), fish and herring gull eggs. K. Betts is a free-lance writer covering environmental science, health and technology (www.kellynbetts.com). According to her website, Ms. Betts holds a B.S. in Environmental Science and an M.A. in Science, Health and Environmental Reporting. The Betts 2009 citation can best be described as an op-ed piece; it is not a review article as that term is typically used.

The papers referred to by Betts utilized gas chromatography-mass spectrometry. DfE should take into consideration when assessing reports of DBDPEthane's environmental detection, that the chemical is not suited to analysis by gas chromatography. It is a high molecular weight, high melting point solid with high adsorptive properties. Laboratory contamination is an issue, as is adsorption to chromatography columns and resultant carry-over. DBDPEthane is better suited to HPLC analysis.

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[48] Comber et al. 2005. PBT Discussion Paper for the European Union TEC NES Subgroup.

Please note that alleged detection of DBDPEthane in seagulls and herring gull eggs by Betts (2009) refers to one publication, e.g. Gauthier et al. 2009[49], that reported on gull eggs only. Reported concentrations (ng/g ww) for the year 2006 at the seven gull colonies monitored were 9.3, n.d. (not detected), n.d. 44, n.d. n.d., and n.d. Five of the 7 seven colonies sampled in 2006 had no detectable DBDPEthane. Table S5, Gauthier et al., for the years 1982-2006 is reproduced below (The 2 detects in 2005 are clearly outliers). This data does not indicate bioaccumulation.

Table S5. Temporal dataset for concentrations (ng/g ww) of decabromodiphenyl ethane (DBDPE) measured in herring gull egg po

from 1982 to 2006 for seven representative colonies on the Laurentian Great Lakes.

	Herring Gull Colony						
Year	Agawa Rocks (L. Superior)	Gull Is. (L. Michigan)	Channel-Shelter Is. (L. Huron)	Chantry Is. (L. Huron)	Fighting Is. (Detroit R.)	Niagara R. (above falls)	Toronto Harbour (L. Ontario)
1982	n.d.	n.d.	n.d.	n.a.	n.d.	n.d.	n.d.
1987	n.d.	n.d.	n.d.	n.a.	n.d.	n.d.	n.d.
1992	n.d.	n.d.	n.d.	n.a.	n.d.	n.d.	n.d.
1995	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
1996	n.d.	n.d.	n.d.	n.d.	n.d.	1.3	n.d.
1997	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
1998	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
1999	n.d.	10	n.d.	n.d.	n.d.	n.d.	n.d.
2000	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
2001	n.d.	11	n.d.	n.d.	n.d.	n.d.	n.d.
2002	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
2003	n.d.	n.d.	n.d.	n.d.	3.2	n.d.	n.d.
2004	n.d.	n.d.	n.d.	11	n.d.	n.d.	n.d.
2005	4.3	104	n.d.	288	n.d.	n.d.	n.d.
2006	9.3	n.d.	n.d.	44	n.a.	n.d.	n.d.

n.a., sample not available.

n.d., is not detected (i.e. < 3 times the standard deviation of the noise).

The publication reporting detection in Lake Winnipeg aquatic species used a nonspecific method, e.g. the bromide ion (m/z = 79, 81 (Law et al. 2006).[50] DBDPEthane was reported as less than the method detection limit (< MDL), e.g. not detected, in 3 of the 8 aquatic species tested. Nondetectable levels were reported in each of the 5 aquatic species where its detection was reported. The highest amount detected was 2.71, 1.51, 1.63, 0.24 and 3.30 ng/g lipid weight in these 5 aquatic species. This data does not indicate bioaccumulation.

See Hardy and Ranken (2008) who question the reported detection in giant panda and Banasik et al.2011 who questioned mass spectrometry interpretation by several of the co-authors on the panda paper.

[49] Gauthier et al. Temporal trends and spatial distribution of non-polybromianted diphenyl ether flame retardants in the eggs of colonial populations of great lakes herring gulls.

[50] Law et al. Bioaccumulation and trophic transfer of some brominated flame retardants in a Lake Winnipeg (Canada) food web. Environ Toxicol Chem 25:2177-2186.

As the term is used in the published literature, 'bioaccumulation' typically refers to the simple detection of a substance in an organism without reference to the dose. If DBDPEthane were actually detected in wildlife as reported in the literature, such detection does not indicate 'bioaccumulation' as defined in the regulatory sense.

List of Appendices

1. Van Hoven et al. 1999. Saytex 8010: Determination of the n-octanol/water partition coefficient by the generator column method. Wildlife International, LtD. Easton, MD.
2. Hardy M. 2006. Response To Reviewers' Comments On The UK's June 2006 Draft For Peer Review Environmental Risk Evaluation Report: 1,1'-(Ethane-1,2-diyl)bis[penta-bromobenzene] (CAS no. 84852-53-9).
3. Black S. 2012. Pharmacokinetic studies of [14C]Decabromodiphenyl ethane (EBP). RTI/0212983.001.002. RTI International, Research Triangle Park, NC.

Albemarle

Comment: Comments on the DRAFT of July 2012 Design for Environment Screening Level Hazard Assessment of Ethylene Bis-Tetraromophthalimide (EBTBP); CASRN 32588-76-4

The materials referenced in the "List of Appendices" are available upon request by contacting Emma Lavoie at lavoie.emma@epa.gov or 202-564-0951.

COMMENTS

DRAFT of July 2012

Design for the Environment Screening Level Hazard Assessment of Ethylene Bis-Tetraromophthalimide (EBTBP); CASRN 32588-76-4

Page 4-311. Screening Level Hazard Summary. This reviewer generally agrees with DfE's summary assessment for EBTBP with the following exceptions: Analog, Carcinogenicity, Neurological, and Bioaccumulation. DfE bases its assessment of EBTBP potential carcinogenicity and neurotoxicity on Decabromodiphenyl Ether (DecaBDE). DecaBDE is not a structural analog of EBTBP. Their structures are very different as illustrated in Figures 1 and 2.

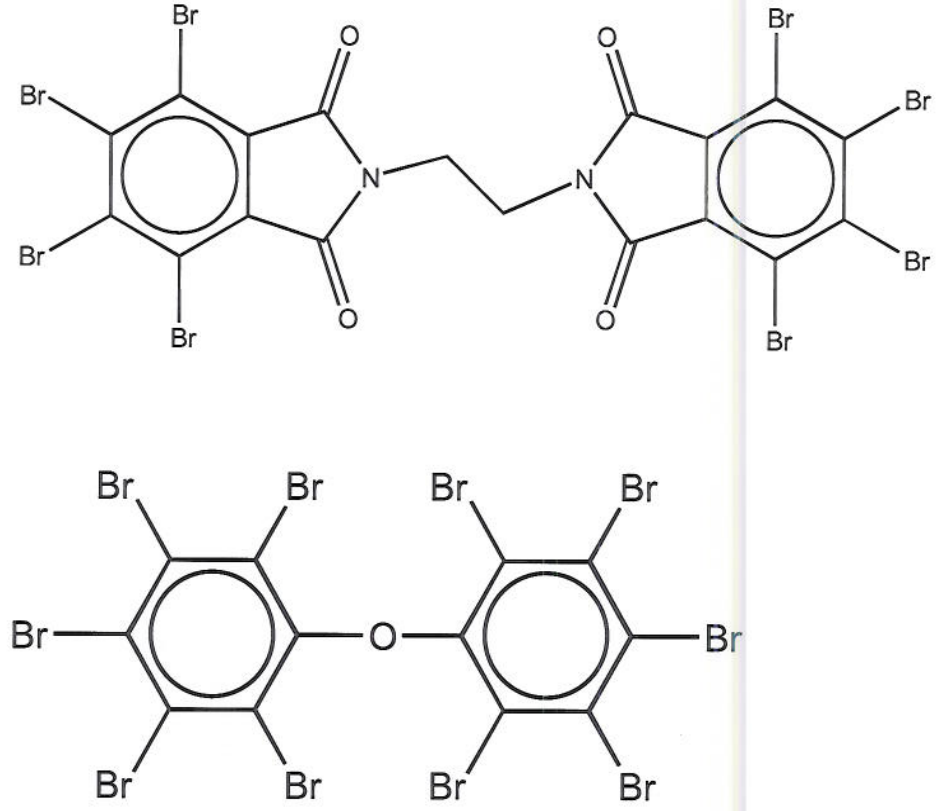

Figure 1. Two-dimensional structures of EBTBP (upper) and DecaBDE (lower).

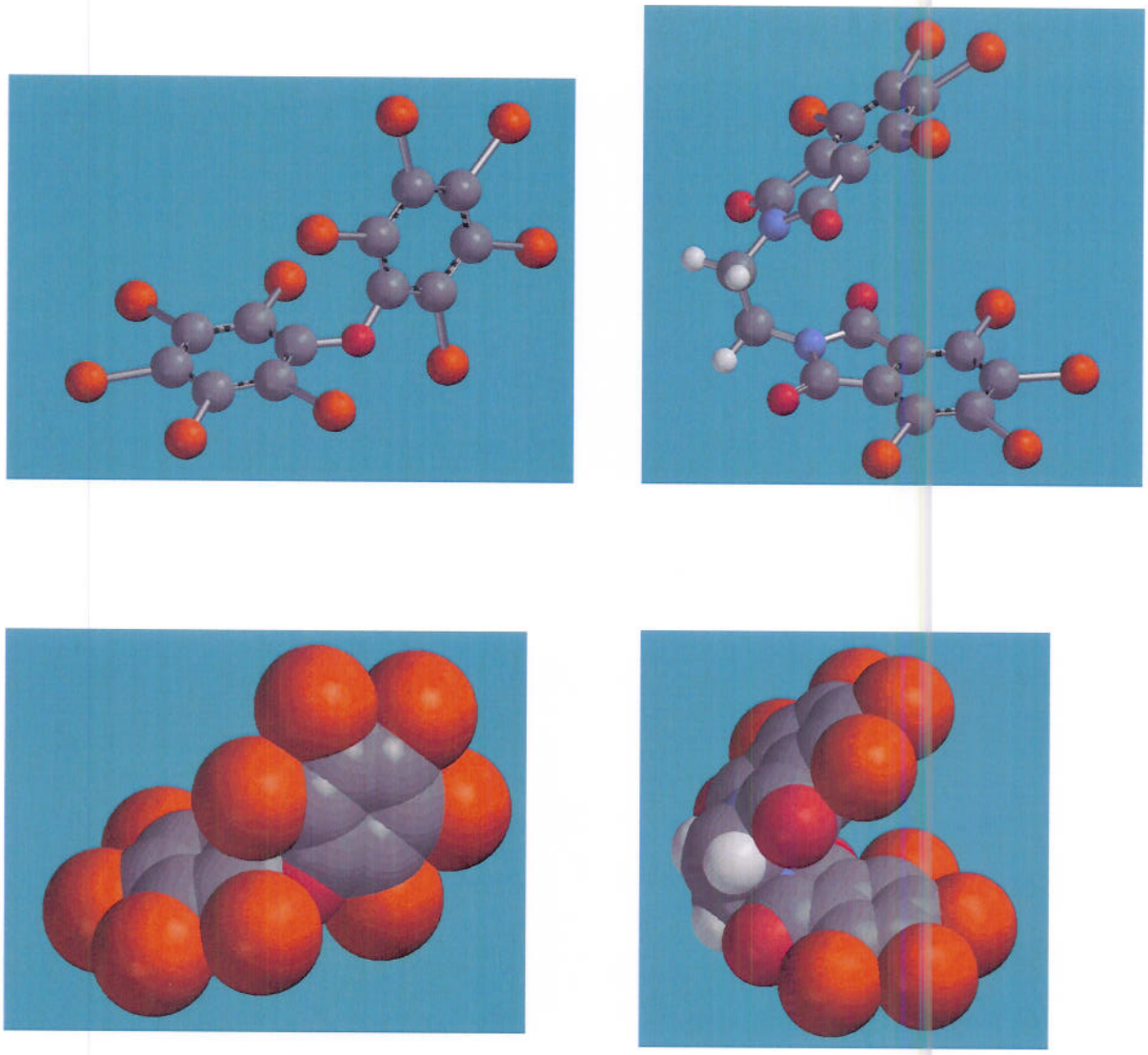

Figure 2. Three-dimensional structures of DecaBDE (l) and EBTBP (r). Orange spheres represent bromine atoms, red spheres oxygen atoms, and blue spheres nitrogen atoms.

In reply to comments submitted as EBTBP's manufacturer in March 2012, DfE responded that "In the absence of experimental data for EBTBP (MW 952), DecaBDE (MW 959) another highly brominated flame retardant was selected by experts in EPA's OPPT as an analog for the assessment of some human health endpoints that were lacking experimental data."

DfE's response mentions two similarities between DecaBDE and EBTBP, e.g., molecular weight and bromine content, but provides no explanation as to why EPA considers DecaBDE is a suitable analog to EBTBP. The two molecules are structurally dissimilar. One is based on

diphenyl ether and the other based on phthalimide. DecaBDE consists of 12 carbon, 1oxygen and 10 bromine atoms (plus relevant hydrogen atoms). EBTBP consists of 18 carbon, 4 oxygen, 2 nitrogen, and 8 bromine atoms (plus relevant hydrogen atoms). DecaBDE exists as one conformer with the aromatic rings orthogonal to one another with an approximate 120° angle (see Fig 2). The 10 bulky bromine atoms on two aromatic rings separated only by an ether linkage due not allow multiple configurations. EBTBP has multiple conformers with the most stable (shown in Fig 2) in a highly folded shape at the ethylene bridge. The angle between the two aromatic rings is acute.

Molecular size differences also exist between DecaBDE and EBTBP (Table 1). The EBTBP is even larger than DecaBDE. DfE must explain why DecaBDE is a suitable analog for the EBTBP molecule beyond molecular weight and presence of bromine atoms, prior to making comparisons.

Table 1. Comparison of the molecular size of EBTBP and DecaBDE.*

Property	EBTBP		DecaBDE
	Most Stable	Least Stable	
Smallest enclosing sphere diameter (Å)	15.69	20.00	15.06
Smallest enclosing cylinder dimension (Å)	11.0	10.4	10.0
Spartan Surface area ($Å^2$)	466	473	390
Spartan Volume ($Å^3$)	452	452	371

*Dimensions were calculated as described in Louwen and Stedeford. 2011[1], and performed September 2012. Surface area and volume were calculated using Spartan based on the quantum mechanic calculated structures

DfE also compared EBPTP to confidential analogs, and reached opposite conclusions from the comparison to DecaBDE. The comparison to confidential analogs resulted in "marginal potential for oncogenicity" and no/low absorption. DfE's comparison to DecaBDE resulted in MODERATE hazard potential for carcinogenicity, neurological and bioaccumulation hazard. Thus, DfE's comparison of EBTBP to DecaBDE is not trivial. DfE must provide valid science-based reasons for this comparison beyond molecular weight and bromine number, if the comparison to DecaBDE is included, and a qualified organic chemist should be consulted. Albemarle Corporation considers a comparison to DecaBDE is not appropriate, and should be deleted.

Page 4-313. Vapor Pressure. EBTBP's vapor pressure has been determined in a guideline/GLP-compliant test using the spinning rotor gauge to be 2.27×10^{-4} Pa at 20°C.[2] The final report is being submitted.

[1] Louwen and Stedeford. 2011. Toxicology Mechanisms and Methods 21(3):183-192.
[2] Lezotte and Nixon. 2005. Determination of the vapor pressure of Saytex BT93 using the spinning rotor gauge method. Wildlife International, Ltd. Easton, MD. APPENDIX 1.

Page 4-313. Log Kow. We suggest adding the following information:

> Albemarle Corporation working with Wildlife International, Ltd was unable to measure EBTBP's water solubility or log Kow, despite extensive efforts, due to insufficient solubility in either organic solvents or water. Preliminary work in 2004/05 for a definitive water solubility study showed EBTBP demonstrated no significant solubility (<10 ppm) in water or 12 different organic solvents: acetonitrile, methanol, ethyl acetate, dichloromethane, tetrahydrofuran, dimethyl formamide, acetone, isopropyl alcohol, isooctane, dibromoethane, toluene, diphenyl ether. Without a solvent, analytical determination of EBTBP's water solubility or octanol-water partition coefficient was not possible.
> Albemarle Corporation subsequently attempted to measure EBTBP's solubility in octanol using a nonspecific method, e.g. total bromine content via X-ray fluorescence spectroscopy. EBTBP's solubility in octanol was 0.4 or 0.6 mg/L[3] using this method. The letter report on the octanol solubility study is attached.

Page 4-315. Carcinogenicity. Albemarle Corporation provided DfE with the following information in March 2012:

> "The draft DfE document rates EBTBP as of MODERATE concern for carcinogenicity. The carcinogenicity summary, page 10, "estimated to be a marginal concern for carcinogenicity based on professional judgment" suggests a LOW hazard. The marginal concern was based on "closely related confidential analogs with similar structures, functional groups, and physical/chemical properties" (page 13, DfE's initial draft hazard assessment). We cannot comment on this given the confidential nature of the analogs. In contrast, the "potential for carcinogenicity" was based on comparison to DecaBDE (page 14). As indicated earlier in this document, EBTBP and DecaBDE are not analogs. Their structures are not similar, and basing a concern for carcinogenicity on DecaBDE is not appropriate. Further, the results of DecaBDE's two-year carcinogenicity studies in rats and mice (NTP 1986) are not of concern for carcinogenicity. The doses were excessive, e.g. Up to 2,550 mg/kg/d in rats and up to 7,780 mg/kg/d in mice. Nevertheless, the extremely high doses did not affect mortality or body weight. NTP reported some, equivocal or no evidence of carcinogenicity in male and female rats and mice, and does not list DecaBDE on its list of carcinogens. Except for EPA's IRIS program, none of the authoritative organizations listed by DfE indicate a concern for carcinogenicity from DecaBDE. Finally, DecaBDE is not mutagenic, and a two-year carcinogenicity study in rats using a lower purity DecaBDE product found no evidence of carcinogenicity at a top dose of 1 mg/kg/d. Please see our comments on the draft DfE document on DecaBDE for details. Given the negative mutagenicity results and the marginal concern expressed, EBTBP should be of LOW concern for carcinogenicity. A concern for bioaccumulation is not appropriate given the lack of bioaccumulation observed in rats. EBTBP's molecular properties and probably low uptake."

DfE's reply to the above was identical that regarding using DecaBDE as an analog for EBPTP:

[3] Albemarle Corporation Memorandum, Dated May 9, 2005. APPENDIX 2.

> "In the absence of experimental data for EBTBP (MW 952), DecaBDE (MW 959) another highly brominated flame retardant was selected by experts in EPA's OPPT as an analog for the assessment of some human health endpoints that were lacking experimental data."

The September draft DfE document again rated EBTBP as MODERATE for oncogenicity (page 4-315). Two ratings were provided, e.g., "marginal potential for oncogenicity" and "potential for carcinogenicity. Both were based on analogy and professional judgment. Marginal potential was based on professional judgment of comparison to "closely related confidential analogs with similar structures, functional groups, and physical/chemical properties". Potential for carcinogenicity was based on professional judgment of the faulty comparison to DecaBDE. DfE's faulty comparison resulted in MODERATE concern for carcinogenicity for EBTBP despite an estimation of "marginal potential for oncogenicity" that was "based on closely related confidential analogs with similar structures, functional groups, and physical/chemical properties".

As discussed previously, DecaBDE is not a suitable analog for EBTBP. DfE's decision to rate EBTBP as MODERATE is not transparent. DfE must explain how professional judgment resulted in widely varying assessments, and why the Agency considers DecaBDE a suitable analog for EBTBP. DfE must also explain how "potential for carcinogenicity" and "marginal potential" translate into a rating of MODERATE in the absence of experimental data from a two-year study on a nongenotoxic substance.

DfE's assessment criteria for carcinogenicity refers to EPA's Guidelines for Carcinogen Risk Assessment, 2005, as a source for data interpretation. That document, page 2-25, states with respect to analogues:

> **2.2.3. Structural Analogue Data**
>
> For some chemical classes, there is significant available information, largely from rodent bioassays, on the carcinogenicity of analogues. Analogue effects are instructive in investigating carcinogenic potential of an agent as well as in identifying potential target organs, exposures associated with effects, and potential functional class effects or modes of action. All appropriate studies should be included and analyzed, whether indicative of a positive effect or not. Evaluation includes tests in various animal species, strains, and sexes; with different routes of administration; and at various doses, as data are available. Confidence in conclusions is a function of how similar the analogues are to the agent under review in structure, metabolism, and biological activity. It is important to consider this confidence to ensure a balanced position.

EPA's guidance document indicates that confidence in conclusions drawn from analogues is a function of the analogues' similarity. EPA's own guidance on carcinogen assessment suggests low confidence in conclusions drawn by comparing DecaBDE and EBTBP due to their dissimilar structures.

EPA's Guidelines for Carcinogen Risk Assessment, 2005, also indicated that other key data are important in the hazard assessment and characterization of carcinogenicity. Among those are physical/chemical properties:

> **2.3.1. Physicochemical Properties**
>
> Physicochemical properties affect an agent's absorption, tissue distribution (bioavailability), biotransformation, and degradation in the body and are important determinants of hazard potential (and dose-response analysis). Properties that should be analyzed include, but are not limited to, molecular weight, size, and shape; valence state; physical state (gas, liquid, solid); water or lipid solubility, which can influence retention and tissue distribution; and potential for chemical degradation or stabilization in the body.

EBTBP's molecular size, weight and lack of solubility limit exposures, and therefore impact the potential for carcinogenicity. DfE did not take this into consideration when assigning a MODERATE rating.

Based on the above, EBTBP is properly rated LOW for cacinogenicity based on limited solubility and large molecular size leading to limited uptake and systemic exposure, negative genotoxicity, and professional judgment to closely related confidential analogs with similar structures, functional groups, and physical/chemical properties.

Page 4-319. Neurotoxicity. DfE rated EBTBP as of MODERATE concern based on analogy to DecaBDE. The data cited for DecaBDE was "Mice as neonates (day 3, 10, 19), single oral dose; neurobehavioral effects". This refers to the Viberg neonatal mice studies.
As discussed previously, DecaBDE is not a suitable analog for EBTBP. Beyond this, however, DfE did not take into consideration a guideline/GLP-compliant developmental neurotoxicity study of DecaBDE has been completed. The NOAEL in that study was 1,000 mg/kg/d, the highest dose tested and administered to maternal rats over gestation and lactation.[4] Both the final report and the peer-reviewed publication of the study have been submitted to EPA. Therefore, DfE's MODERATE rating for EBTBP based on DecaBDE's assumed neurotoxicity has been refuted.

We also note that the experimental design used in the Viberg studies has been found unacceptable by authors affiliated with EPA[5], whereas authors affiliated with EPA concluded studies performed according to the developmental neurotoxicity guideline represent the best science for assessing the potential for such effects.[6]

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[4] Biesemeier et al. 2011. An oral developmental neurotoxicity study of decabromodiphenyl ether (DecaBDE) in rats. Birth Defects Research Part B 92:17-35.

[5] Holson et al. 2008. Statistical issues and techniques appropriate for developmental neurotoxicty testing: a report from the ILSI Research Foundation/Risk Science Institute expert working group on neurodevelopmental endpoint. Neurotoxicol Teratol 30:326-348.

[6] Makris et al. 2009. A retrospective performance assessment of the development neurotoxicity study in support of OECD test guideline 426. Environ Health Perspect 117:17-25.

DfE cannot utilize a concern for DecaBDE to impose a MODERATE hazard on EBTBP. Given that EBTBP's low solubility, large molecular size, and high molecular weight limit exposures and the absence of data suggesting effects, EBTBP should be rated as of LOW concern.

Page 4-325. Bioaccumulation. Summary. EBTBP was rated as HIGH based on DfE's statement that its assessment criteria indicate that an estimated BAF will be used when a single *measured* BCF value is available. DfE also said that EBTBP's estimated BAF is consistent with that anticipated for high MW chemicals with a high degree of bromination. The DfE draft document is incorrect in both instances.

1. Two measured values are available for EBTBP. Both are < 100.

2. DfE's assessment criteria for the alternatives program[7], page 40, states that "Modeled data from sources such as EPI Suite™ [25] are acceptable when data are unavailable". According to DfE's assessment criteria, modeled data are *acceptable* when experimental data are *unavailable*. Two experimental values are available for EBTBP, and the modeled estimate should not be used.

3. DfE's assessment criteria make no provision for a more conservative hazard designation. DfE's draft document on DecaBDE alternatives, page 4-23, states:

> Experimental BAF or BCF values can be compared directly to the DfE criteria for this endpoint to assign a hazard designation. The BCF/BAF designations range from <100 for a Low designation to >5,000 for a Very High Designation (see 4.1.2). If experimental values were available for both of these endpoints, and the BCF and BAF were >100 (i.e., above the Low designation), the largest factor was used to assign hazard designation. If experimental BCFs <100 were available, the estimated upper trophic BAF from EPISuite™ was used preferentially if its use resulted in a more conservative hazard designation and the potential for metabolism was accurately accounted for within the model estimates.

Contradicting its own assessment criteria, DfE arbitrarily substituted an estimated BAF for a measured value. DfE further elected to apply this substitution only to substances for which the measured value is of no concern, e.g. <100. In concluding EBTBP has a HIGH concern for bioaccumulation, DfE did not follow its own criteria.

DfE's assessment criteria, Table A2, page 42, states:

Bioaccumulation (BAF / BCF)	Very High	High	Moderate	Low	
BCF/BAF	> 5,000	5,000 – 1,000	<1,000 – 100	< 100	
Log BCF/BAF	>3.7	3.7-3	<3-2	<2	

EBTBP's measured BCF value is < 100. Based on DfE's assessment criteria, EBTBP is of LOW concern.

[7] Design for the Environment Program Alternatives Assessment Criteria for Hazard Evaluation. V 2.0, August 2011. Office of Pollution Prevention & Toxics. U. S. Environmental Protection Agency.

4. DfE improperly based its assessment of bioaccumulation on an estimated BAF of 170,000. The above text, page 4-23, qualifies that EPISuite's estimated BAF values are usable only if the potential for metabolism was accurately accounted for within the model estimate. Yet; page 4-325 states no data was located on fish metabolism for EBTBP. Therefore, the model cannot be said to accurately account for EBTBP's metabolism and the estimated BAF is unusable.

5. DfE did not provide data or literature citations to support its contention that high molecular weight chemicals with a high degree of bromination are highly bioaccumulative. To the contrary, substances containing numerous bromine atoms are unlikely to bioaccumulate due to a combination of factors.

   i) In the absence of citations, this reviewer suspects DfE's opinion was based on literature reports of DecaBDE's detection in biota. With respect to these literature reports of DecaBDE's detection:

   - The terms 'bioaccumulation' or 'bioaccumulate' were used in many of these reports as synonymous with detection. BAFs were seldom calculated.
   - The trace levels (frequently ng/g lw) reported do not meet regulatory definitions of accumulation.
   - Reports of DecaBDE's detection in environmental biota were based on analytical methods (GC-MS-EI or GC-MS-ECNI) that sacrificed *specificity* for *sensistivity*. These methods were based on detection of the bromine ion (m/z= 79, 81) or the brominated phenoxybenzene ion (m/z= 494.6, 496.6). This methodology is not specific for detection of DecaBDE, but it is highly sensitive. Environmental samples contain a myriad of unknowns, and thus specificity should take priority over sensitivity when assessing nontoxic substances. This has not been done for DecaBDE.
   - DecaBDE is not well suited to analysis by gas chromatography due to its high molecular weight, high melting point, adsorptive properties and limited solubility in organic solvents. Its analysis by GC is challenging and problematic as indicated in multiple publications.
   - Laboratory studies using other techniques (HPLC, liquid scintillation, ion chromatography) do not indicate bioaccumulation.

   ii) DfE's opinion regarding accumulation of highly brominated molecules does not conform to experimental data on three highly ($\geq$ 10 bromine atoms) brominated substances (Table 2). DfE must define how it arrived at this conclusion and allow comment. For example, Burreau et al. 2004[8], cited in Sijm et al. 2007, reported no biomagnification in a Baltic food web for polybrominated diphenyl ethers containing 6 or more bromine atoms.

[8] Burreau et al 2004. Biomagnification of polychlorinated biphenyls (PCBs) and polybrominated diphenyl ethers (PBDEs) studied in pike (*Esox lucius*), perch (*Perca fluviatilis*) and roach (*Rutilus rutilus*) from the Baltic SeaChemosphere 55:1043-1052.

iii) DfE's opinion regarding accumulation of highly brominated substances does not conform to the influence of molecular properties on bioaccumulation potential.

- Multiple factors are important to bioaccumulation: molecular weight, molecular size, molecular charge, speciation, surface/volume ratios, morphology, and biotransformation.[9]
- Absorption is a prerequisite to bioaccumulation. Solubility is a prerequisite for absorption by passive diffusion. EBTBP's lack of solubility in either water or organic solvents is an initial indicator that it will be poorly absorbed.
- Molecular weight influences dietary absorption of chemicals. Chemicals with molecular weights > 600 are poorly absorbed.[10], [11], [12], [13] Absorption efficiency by fish from the diet for chemicals with molecular weight >650 ranged from 'nil' to 0.01. EBTBP's molecular weight is 951.47. It is expected to be poorly absorbed by fish from the diet, and its absorption efficiency is expected to be very low.
- Studies have shown linear correlations between BCF log transformations and a chemical's partitioning between octanol and water.[14] However, the linear relationships between BCF and Kow are not adequate with Log Kow values > 6. EBTBP's estimated Log Kow is 9.8. Thus, EBTBP's log Kow is outside of the linear range, and the traditional assumption regarding a 'high' log Kow translating into a 'high' BCF is unlikely to apply.
- For chemicals with a log Kow > 5.5, factors other than lipophilicity (e.g. solubility in octanol) control bioconcentration. Molecular size is important. Molecular size can be expressed in several ways: cross-sectional diameter, total surface area, molecular volume, dimensional length, etc. EBTBP's calculated dimensions, surface area and volume are shown in Table 2. Niimi and Oliver (1988) reported that chemicals with molecular volumes over 0.3 nm^3 (300$Å^3$) are poorly absorbed. Substances with a cross-sectional diameter of >0.95 nm generally do not bioaccumulate due to limited membrane permeability (Sijm et al. 1993).
- Dimitrov et al. (2002) refined the maximum molecular length to 1.5 nm, e.g. the maximum tolerance of the cell membrane. Chemicals > 1.5 nm (15 Å) long are unlikely to move through the cell membrane. Conformational flexibility also appears important because flexibility can further decrease passage through the membrane and hence decrease uptake.

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[9] Sijm et al. 2007. Chapter 3. Transport, Accumulation and Transformation Processes. In Risk Assessment of Chemicals: An Introduction, pp 73-158. C.J. van Leeuwen and T.G. Vermeire (eds.). Springer.

[10] Niimi and Oliver. 1988. Influence of molecular weight and molecular volume on dietary absorption efficiency of chemicals by fishes. Can J Fish Aquat Sci 45:223-227.

[11] Zitco V 1974. Uptake of chlorinated paraffins and PCB from suspended solids and food by juvenile Atlantic salmon. Bull Environ Contam Toxicol 12:406-412.

[12] Tulp M and Hutzinger O. 1974. Some thoughts on aqueous solubilities and partition coefficients of PCB, and the mathematical correlation between bioaccumulation and physico-chemical properties. Chemosphere 10:849-860.

[13] Bruggeman et al. 1984. Bioaccumulation of super-lipophillic chemicals in fish. Toxicol Environ Chem 7:173-189.

[14] Dimitrov et al. 2002. Predicting bioconcentration factors of highly hydrophobic chemicals. Effects of molecular size. Pure Appl Chem 74(10): 1823-1830.

Table 2. Laboratory studies investigating bioconcentration/bioaccumulation of highly brominated substances.

Chemical	Fish				Other Biota	Reference
	BCF_{water}	BAF_{diet}	BMF	Uptake from Diet		
DecaBDE	<0.3 – 3 6 wks					Japan CSCL Database: http://www.safe.nite.go.jp/jcheck/english/template.action Test material composed of > 75% BDE 209, ca 17% nonaBDEs, ca. 0.8% octaBDEs
				0.005% 120 d		Kierkegaard et al. 1999 Environ Sci Technol 33:1612-1617. Dose = 7 or 10 mg/kg/d
				0 90 d		Stapleton et al. 2004 Envrion Sci Technol 38:112-119. No measurable uptake over 90 d; dose = 940 ng/fish/d
		0.0039		0.39% 112 d		Stapleton et al. 2006. BAF based on cumulative DecaBDE dose and total PBDE reported in fish.
			0.3	0.3% 56 d		Tomy et al. 2004. Environ Sci Technol 38:1496-1504
		~0.02 28 d				Noyes et al. 2011 Tox Sci 122:265-274
					L. variegates 28 d; dose ~ 300 ug/g dry soil. Not detected in worms exposed to biosolids; < LOQ exposed via spiked sediment	Ciparis and Hale 2005 Environ Toxicol Chem. 2005 24:916-25. Commented that bioaccumulation not observed in trout or carp exposed via treated diet (e.g. Kierkegaard & Stapleton studies)
					E. fetidae 28 d; doses 312 – 5000 mg/kg dry soil. Not detected	Aufterheide et al. 2001; GLP/guideline study
					Rat BAF = 0.05 for 21 d dietary exposure	Huwe and Smith 2007 Environ Sci Technol 41:2371-2377; Additions and Corrections 41:4486.
					Rat BAF = 0, 0.06, 0.61 or 0.14 depending on dose & matrix for 21 d dietary exposure	Huwe et al. 2008 Environ Sci Technol 42:2694-2700
					Rat. BAF=0. Not detected in fat or carcass; <= 1% dose in liver; 21 days dietary exposure	Huwe et al. 2008 Environ Sci Technol 42:7018-7024
					Rat BAF rough estimate 0.00007 based on plasma concentration (~1000 ng/g ww) after 15 daily doses of 1000 mg/kg/d	Biesemeier et al. 2010 Drug Metab Dispo 38:1648-1654
Decabromo biphenyl	0.4, 5.4; 6 wks					Japan CSCL Database: http://www.safe.nite.go.jp/jcheck/english/template.action; APPENDIX X.
Tetradecabromodiphenoxybenzene	4.8, 14; 8 wks					Asano Chemicals (1988), Tokyo, Japan; English summary of fish bioconcentration study performed by Kurume Laboratory, Japan.

- EBTBP's molecular volume is > 300Å^3, and thus is expected to be poorly absorbed.
- The EBTBP molecule has 10 possible conformers, and will spend more time in the more stable configurations. EBTBP's most stable conformer is shown in Fig 2. The longest dimension of its most stable conformer is >1.5 nm, and thus EBTBP is unlikely to move through cell membranes (Table 1).
- EBTBP's most stable conformer is highly folded, which will further decrease passage through membranes.

In conclusion, absorption is required for the expression of bioaccumulation. EBTBP's lack of solubility and large molecular weight, molecular volume, and molecular dimensions indicate it will be very poorly absorbed from the diet. Because the gastrointestinal tract is of finite length, assimilation from food occurs over a finite time frame. It stands to reason that substances with extremely poor absorption efficiency will pass out of the digestive tract prior to being absorbed, and their uptake rate constants (e.g. change in tissue concentration/change in time) will be correspondingly low. Substances that are poorly absorbed rarely accumulate.

(iv) DfE's opinion regarding accumulation of highly brominated substances also did not take into consideration EPA's human health personnel who concluded EBPTP would have no or poor absorption through all routes of exposure based on "closely related analogs with similar structures, functional groups, and physical/chemical properties". Absorption is a prerequisite for bioaccumulation. Substances that have limited bioavailability are unlikely to bioaccumulate.

Based on the above, EBTBP is properly rated LOW concern for bioaccumulation.

List of Appendices

1. Lezotte and Nixon. 2005. Determination of the vapor pressure of Saytex BT93 using the spinning rotor gauge method. Wildlife International, Ltd. Easton, MD.
2. Albemarle Corporation Memorandum, Dated May 9, 2005..

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Toxicology and Applied Pharmacology 202 (2005) 302–308

Toxicology and Applied Pharmacology

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Review

Confounders in interpreting pathology for safety and risk assessment

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Received 30 April 2004; accepted 29 June 2004
Available online 11 August 2004

Abstract

The contribution of pathology to toxicity assessment is invaluable but often not clearly understood. Pathology endpoints are the central response around which human health risk assessment is frequently determined; therefore, it is important that the general toxicology community understand current concepts and nomenclature of toxicologic pathology. Toxicologic pathology encompasses the study of changes in tissue morphology that help define the risk of exposure to xenobiotics. Toxicologic pathology is a discipline that has changed and adapted over time including methods of analysis and nomenclature of lesions. As risk assessments are updated for chemicals in commerce, frequently the older literature must be reviewed and reevaluated. When interpreting pathology data from animal studies, it is important to consider the biological significance of a lesion as well as its relationship to the ultimate adverse health effect. Assessing the potential for a chemical to cause harm to humans must include the examination of the entire pathology database in context of the study design, the mode of action of the chemical of concern, and using the most current interpretation of a lesion to determine the significance for human health effects of a particular tissue response.
Published by Elsevier Inc.

Keywords: Toxicologic pathology; Risk assessment; Xenobiotics

Contents

Introduction

Assessment of the potential for a xenobiotic to cause adverse health effects is a complicated process that requires as full an understanding of the biological impact of a chemical as is possible. An important component of the safety evaluation is the evaluation of the morphologic

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0041-008X/$ - see front matter. Published by Elsevier Inc.
doi:10.1016/j.taap.2004.06.022

changes of organs from rodents after treatment with the chemical of interest. Although in vitro assays and pharmacokinetic studies provide data that enable a more complete mechanistic understanding of the toxicity of a chemical, it is usually the morphologic changes to a tissue or tissues that are used to determine the human health risk of an environmental contaminant or pharmaceutical.

The following discussion presents issues that should be considered whenever evaluating a set of pathology data for determination of human health risk. These issues frequently affect the validity or interpretation of the relevance of a lesion that may be used as the critical effect for risk assessment of a chemical based on its potential effect on human health. Included are variables that affect interpretation relative to study design, significance of a particular lesion, appropriate evaluation of spontaneous lesions, identification and significance of precursor effects, and changes in terminology related to the biology of a lesion.

Interpretation relative to study design

The specific details of the study, its design and animal husbandry can have an effect on the induction and characteristics of tissue alterations. Therefore, tissue changes must be evaluated in light of a thorough knowledge of route of exposure, when dosing stopped before necropsy, availability of food and water, and type of animal housing. Some general well-documented variables to interpretation of a study include wire-mesh vs. shoebox caging, gavage vs. feed vs. drinking water exposure, and fasting vs. nonfasting before necropsy. These specific choices in study design could have a significant impact on the overall study outcome and its interpretation.

As an example, one factor that can have a major, although often unrecognized, impact on results is the number of animals housed in a cage. Caging density can affect chronic changes such as tumor incidence (Haseman et al., 2003; Nyska et al., 1998) as well as short-term effects such as serum hormone levels (Nyska et al., 2002). This can become important as one compares multiple studies of the same chemical given by different routes. Rodents are typically housed individually for inhalation studies whereas in drinking water or feed studies the animals typically are group-housed. There can be a 2-fold difference in tumor incidence between group and individually housed rats (Haseman et al., 2003) and in some cases more (Haseman et al., 1994). In a comparison of individually and group-housed male B6C3F1 mice, both liver and lung tumor incidences were significantly lower whereas combined dermal and skin tumors and lymphomas were significantly greater in group-housed mice (Haseman et al., 1994). Group-housed female B6C3F1 mice had significantly lower incidences of liver tumors and hemangiosarcomas but greater incidences of lymphomas compared to those individually housed (Haseman et al., 1994). Group-housed male F344 rats had a significantly greater incidence of interstitial cell tumors, mononuclear cell leukemia (“Fischer rat leukemia”) and a lower incidence of pheochromocytoma, and tumors of the pituitary gland and pancreatic islets (Haseman et al., 2003). Group-housed female F344 rats had a significantly lower incidence of pituitary gland tumors than singly housed females (Haseman et al., 2003). Caging density can also have an impact on body weight, serum testosterone, estradiol, and corticosterone levels as well as cell proliferation and apoptosis rates in multiple tissues (Haseman et al., 1994, 2003; Nyska et al., 2002). These data illustrate the importance of considering the husbandry of the test species when comparing across studies as well as combining control data to create historical databases.

Another effect of husbandry practice was seen in a study exposing mice to chloroform by inhalation (Larson et al., 1996). In this study, due to animal supply issues, the female mice were started on study 2 weeks before the males. Male mice were then brought into the animal rooms a week before the second interim time point (3 weeks on study) resulting in a stimulatory effect on the females such that the proliferation rate of hepatocytes doubled in the control female animals (Larson et al., 1996). A similar response was reflected in all the treatment groups. While this effect was gone by 6 weeks on study it did make it difficult to interpret the hepatocyte proliferation differences between 3 weeks and the rest of the time points within each concentration group (Larson et al., 1996).

Toxicologists frequently interpret data based on total chemical consumption or concentration × time. However, the dosing regimen can have an impact on tissue response. Mice exposed to 10 or 90 ppm chloroform by inhalation for 13 weeks had different responses depending on if the exposure was for 7 or 5 days/week (Larson et al., 1996). Male mice after 13 weeks had similar lesion scores in the kidneys regardless of exposure regimen but the cell proliferation rate was several fold higher in male mice exposed 5 days/week compared to 7 days/week. In the same study, female mice had more severe hepatotoxicity and several fold greater hepatocyte proliferation rates when treated 7 days/week compared to 5 days/week (Larson et al., 1996). These data illustrate that dosing schedules can have both a biologically and statistically significant effect on tissue response and interpretation of the study.

Similarly, the length of time between the last dose of a chemical and necropsy can lead to a different interpretation although similar studies overall were performed (Medinsky et al., 1999; White et al., 1995). When rats and mice were exposed to ETBE by inhalation, one study had no histopathology (White et al., 1995) whereas a second study reported several tissues with microscopic alterations (Medinsky et al., 1999). The likely reason for this discrepancy was due to the length of time between the last exposure and necropsy. In a traditional inhalation toxicity study, the animals are exposed 5 days/week with necropsy starting on

the Monday following the last exposure (60 h or longer after final exposure) and lasting several days (White et al., 1995). Whereas, if one has the necropsies always within 24 h of the last exposure, then there may be insufficient time for complete tissue repair to occur (Medinsky et al., 1999). The length of time between the last exposure and necropsy is important not only for understanding the significance of microscopic alterations but also in interpreting other endpoints such as cell proliferation, accumulation of cellular proteins such as α2 u-globulin, and transcriptional or protein analysis (i.e., genomics and proteomics).

Lesion significance

Much has been written on identifying adverse effects and whether a particular tissue response should be considered adverse or not. For a recent overview on this topic and approach to determine adversity the reader should consult Lewis et al. (2002). We would suggest that deciding whether a tissue alteration is biologically relevant is as important as determining whether or not it is adverse. By this we mean, does it provide information regarding the mode of action of the xenobiotic's toxicity or carcinogenicity or does it provide information about biological plausibility as it relates to human health risk assessment? In some cases, a tissue alteration that is not adverse can provide important information on how lesions that are considered adverse developed, and therefore the seemingly incidental alteration is highly relevant.

An excellent example of this approach is in interpreting the significance of the mouse liver tumor response after chronic exposure to unleaded gasoline. Female, but not male, B6C3F1 mice exposed to wholly vaporized unleaded gasoline for 18 months had an increased incidence of liver tumors (MacFarland et al., 1984). The liver tumor incidence in male mice was 45%, 36%, 45%, and 44% for control, low, mid, and high dose, respectively, and 14%, 19%, 21%, and 48% for female mice. In female mice exposed to the high concentration, the tumor incidence was increased to the male background tumor incidence. This observation stimulated reexamination of the study (MacGregor et al., 1993; Magaw et al., 1993). This re-review of the original study reported that female mice had a decreased severity of cystic endometrial hyperplasia with increasing exposure concentration and uterine atrophy in mice exposed to the highest concentration (MacGregor et al., 1993). This resulted in the hypothesis that the unleaded gasoline was masculinizing the female mice which could account for the increased incidence in liver tumors (MacGregor et al., 1993). Additional work showed that unleaded gasoline was acting as an antiestrogen by enhancing the metabolism of estrogen in the tissues (Standeven and Goldsworthy, 1994; Standeven et al., 1994a). Estrogen inhibits liver tumor development in female mice and therefore loss of this protective effect allowed spontaneously intitiated cells to develop into tumors (Moser et al., 1996; Standeven and Goldsworthy, 1993; Standeven et al., 1994b). Therefore, in exposure of female mice to unleaded gasoline, the decreased cystic endometrial hyperplasia was an incidental change, and certainly not an adverse effect, that provided the clue to a proposed mechanism for liver tumor development.

Spontaneous lesions

Numerous spontaneous lesions have been described in rodent studies. The development of spontaneous lesions may also be influenced by exposure to xenobiotics. In some cases, the influence may be as a result of the decreased or increased palatability a compound may impart to the water or feed resulting in changes of incidence or severity from changes in caloric consumption. However, more commonly, an increase in incidence and/or severity of a spontaneous lesion is from enhancement of the tissue alteration that is a key event in the pathogenesis of the spontaneous lesion. A common example is the effect many chemicals have on chronic progressive nephropathy in the rat.

Chronic progressive nephropathy (CPN) is one of the most frequently diagnosed lesions in toxicity studies utilizing rats (Goldstein et al., 1988; Hard and Khan, 2004; Seely et al., 2002). The lesion is most often diagnosed in studies that are of longer duration such that the rats are over a year of age at the termination of the study, although lesions associated with this syndrome are sometimes reported in studies of much shorter duration such as 13 weeks or less. The complete pathogenesis of this syndrome has not been definitively determined; however, there are specific tissue alterations that are always associated with its development (Goldstein et al., 1988; Hard and Khan, 2004; Seely et al., 2002). These tissue changes include thickened basement membranes, tubular necrosis, tubular regeneration, interstitial fibrosis, and inflammation (Goldstein et al., 1988). Therefore, any xenobiotic that directly damages any part of the kidney, particularly the cortical tubules, can result in an increased incidence and severity of this diagnosis. It is therefore important to be able to separate spontaneous CPN from both CPN enhanced by xenobiotic toxicity and from renal toxicity unrelated to CPN (Hard and Khan, 2004).

The morphologic alterations that are included in the diagnosis of CPN are qualitatively the same regardless of whether the lesion is spontaneous or secondary to long-term exposure to a renal toxicant (Hard and Khan, 2004; Montgomery and Seely, 1990). In many cases, particularly in the older literature, only the incidence of CPN is reported. While sometimes incidence alone may be sufficient to identify a treatment effect, it is rarely adequate to determine if a nephrotoxicant enhanced the development of this spontaneous lesion. The only method available to describe the degree of an enhancing effect is by using severity scores which typically indicate how much of the kidney is effected

by CPN allowing a better characterization of the contribution the xenobiotic made in kidney damage (Shackelford et al., 2002). This is particularly important in chronic studies where spontaneous lesion incidence, especially CPN, can be 100%.

The growth, development, and occurrence of many lesions can be affected by husbandry such as caging density, diet, and types of caging or bedding (Bolon et al., 1991; Gamble and Clough, 1976; Haseman et al., 2003; Keenan et al., 1995, 1997, 2000). An example is the cage-contaminant lesions of the nose and trachea that are secondary to ammonia vapors from urine collecting in cages with an inappropriate amount or type of bedding (Bolon et al., 1991; Gamble and Clough, 1976). Normal animal behavior can have an impact on many aspects of a study. It has long been known that male mice have a tendency to physically interact in an aggressive manner when group-housed (Wimer and Fuller, 1968). These interactions can be as mild as excessive grooming or barbering to extreme episodes of fighting resulting in death of a cage mate (NRC, 1996; Stark and Ostrow, 1991; Van Loo et al., 2003). This behavior is typically only present in male mice and rarely if ever present in female mice or rats (NRC, 1996; Stark and Ostrow, 1991). Clearly, this aggressiveness in mice is due to testosterone and can vary dependent on the strain of mouse (Brain and Bowden, 1979; Miczek et al., 2001; Van Loo et al., 2003; Wimer and Fuller, 1968). Fighting can result in wounds to the skin over large areas of the body which can affect behavior, general health, and the ability to eat or drink including standing to reach the food or water, all of which can effect the group means reported in the summary tables. However, there are ways, if properly employed, that can avoid these potentially confounding behaviors (Van Loo et al., 2003).

The complete description of a spontaneous lesion, including both incidence and severity, is frequently critical to make an appropriate interpretation of the data. Rats treated with chloroform in the drinking water for up to 2 years developed renal cortical tumors (Jorgenson et al., 1985). It was not possible to determine what role nephrotoxicity had in the development of the renal tumors as only incidence of CPN was reported, with all treatment groups having 90–100% incidence at the termination of the study (Jorgenson et al., 1985). This information became critical because of the proposed mode of action for chloroform-induced cancer (Templin et al., 1996; Wolf and Butterworth, 1997). After reevaluation of the original slides, this time providing a severity score for CPN, it was discovered that the severity of CPN actually decreased with dose (Hard et al., 2000). The decreased palatability of the drinking water at the higher doses of chloroform resulted in decreased water and food intake, lower body weight and caloric restriction protected the high-dosed rats from the development of spontaneous CPN (Hard et al., 2000). It then became possible to separate the renal alterations associated with spontaneous CPN from those caused by exposure to chloroform resulting in a more appropriate interpretation of the study (Hard et al., 2000).

It has long been suggested that in rats with more severe CPN there is a greater likelihood for tumors to develop; however, there are few data to support this assertion. Recently, it has been reported that indeed there is a small, but statistically significant, association between the presence of renal tumors and severe nephropathy (Seely et al., 2002). This finding is important in evaluating the biological relevance of a slight increase in incidence of rat renal tumors in a study where the renal tumor response is associated with severe nephropathy. For example, rats treated with hydroquinone or ethyl benzene both had increased renal tumor incidence in association with increased severity of CPN (Hard, 2002; Hard et al., 1997). More specifically, the preneoplastic lesions and tumors arose from within the areas of CPN and primarily occurred only in kidneys from rats with the most severe CPN lesion scores (Hard, 2002; Hard et al., 1997). These data suggested a direct association between chemically enhanced CPN and tumor development.

Recently, a proposal has been made for utilizing specific criteria to determine the relevance of rat renal tumors that occur at low incidence, but above background, in association with enhanced CPN (Hard and Khan, 2004). It was suggested, that in this case, these renal tumors are secondary to severe CPN rather than a direct response of chemical exposure. These criteria are: (1) the chemical must exacerbate CPN to very advanced lesions or end-stage kidney disease; (2) the tumors are all small adenomas or borderline hyperplastic/small adenomatous lesions; (3) these lesions are only present in kidneys with the greatest CPN severity; (4) the preneoplastic foci are restricted to CPN affected kidney; and (5) there is no evidence of renal cellular injury in kidney unaffected with CPN (Hard and Khan, 2004). Using this approach, it was determined that the renal tumors induced by hydroquinone and ethyl benzene were associated with severe CPN but the renal tumors present after chloroform exposure were not (Hard, 2002; Hard et al., 1997, 2000). It was therefore proposed that because there is no direct correlate between the spectrum of lesions of rat CPN and human renal disease, in the case where a small increase in renal tumor incidence can be directly linked with exacerbated CPN, the renal tumors may not be relevant for human health risk assessment (Hard and Khan, 2004).

Identification of a precursor effect

Frequently, changes are identified in tissues, or from serum analysis, that are not in themselves adverse or even indicators of disease, but rather suggest a change that, if treatment is continued or given at a much greater dose, would develop into an adverse health effect. Examples of this are the salts of chlorate and perchlorate which

competitively inhibit iodine uptake. When iodine uptake is sufficiently inhibited for long periods of time, then circulating thyroxine and triiodothyronine levels can dramatically decrease and thyroid stimulating hormone increase (Capen, 1996). This would be considered clinical hypothyroidism which would be a significant adverse health effect. With continued exposure, proliferative changes can occur and, in rats, tumors may arise (Capen, 1996; Capen et al., 2002; Hardisty and Boorman, 1990).

When a toxicity pathway is well described it may then be sufficient to show that a biologically relevant precursor effect is present to support concern about the likelihood of downstream adverse health effects (Hooth et al., 2001). In the case of thyroid endocrine disruptors, these effects could include hypothyroidism and fetal neurodevelopmental deficits (Zoeller, 2003; Zoeller et al., 2002). This particular toxicity pathway does not have to go to its conclusion in order for identification of the potential for an adverse response to be possible. Histologic changes that occur, and that would be considered precursor effects, include decreased amounts of thyroglobulin colloid within thyroid gland follicles and follicular epithelial cell hypertrophy. These changes can be detected very early and can be specifically associated with thyroid endocrine disruption. In rats treated with chlorate or perchlorate, the iodine uptake inhibition initially causes colloid depletion and hypertrophy (Hooth et al., 2001; Siglin et al., 2000; York et al., 2001a, 2001b). These changes are associated with thyroid hormone alterations and, although considered precursor alterations, certainly indicate that if exposure continued then adverse effects could result.

Changing terminology

In toxicologic pathology, one frequently discovers that the name of a lesion changes although the morphology stays the same. This is typically from advancements in science and greater understanding of how tissue alterations develop, particularly cancer. In performing risk assessments, the assessor must review all the data available, which frequently may have been collected and published years or decades previous. However, the interpretation of the data must be based on the most recent terminology and the current understanding of a particular lesion's biological significance. The evaluation of older literature must take into account changes in terminology and the current knowledge and thinking on the significance of a lesion.

An example of the impact these changes in terminology and interpretation can have on a series of lesions is the histopathology of rodent liver tumors. Nonmalignant masses that arise from proliferating initiated hepatocytes have been variously called "neoplastic nodules", "benign hepatoma", "hepatoma", "hepatocellular adenoma", and "nodular hyperplasia" (Bannasch and Zerban, 1990; Eustis et al., 1990; Frith et al., 1994; Harada et al., 1999; Maronpot et al., 1987; Schauer and Kunze, 1976; Squire and Levitt, 1975; Turusov and Takayama, 1979). Besides changes in terminology and understanding of the biology of what is currently called hepatocellular adenoma, the significance of foci of cellular alteration have also changed (Bannasch and Zerban, 1990; Eustis et al., 1990; Frith et al., 1994; Harada et al., 1999; Maronpot et al., 1987; Squire and Levitt, 1975).

Initially, it was thought that benign hepatocellular tumors did not occur in rats, that all neoplastic hepatic masses in rodents had the potential to become malignant, and so the terms hepatoma and adenoma were not appropriate. Therefore, the term neoplastic nodule was recommended (Squire and Levitt, 1975). Over time as the biology of these masses was better understood and reversibility studies were performed, showing that some lesions called neoplastic nodules regressed when chemical treatment was stopped, it was suggested that the terminology needed to be changed to reflect the biology (Maronpot et al., 1987). The terms neoplastic nodule, benign hepatoma, and hepatoma were all eliminated from the standard lexicon and replaced with hepatocellular adenoma. It was also determined that the term nodular hyperplasia or hyperplasia should only be used for a nonneoplastic regenerative proliferation of hepatocytes after recurrent or persistent cytotoxicity such as is present in cirrhotic livers (Maronpot et al., 1987). This approach is now the generally accepted nomenclature for benign hepatocyte tumors (Bannasch and Zerban, 1990; Eustis et al., 1990; Frith et al., 1994; Harada et al., 1999). The nomenclature for description of and biological understanding of hepatocelluar carcinoma has stayed fairly constant over this same period of time (Eustis et al., 1990; Harada et al., 1999; Squire and Levitt, 1975).

Another liver lesion whose significance, interpretation, and nomenclature has changed is the focus of cellular alteration. The histologic detection of these foci is based on the tinctorial qualities and apparent texture of the cytoplasm of affected hepatocytes (Bannasch and Zerban, 1990; Frith and Ward, 1980; Frith et al., 1994; Maronpot et al., 1987; Schauer and Kunze, 1976; Squire and Levitt, 1975). The term *foci/focus* and *area* have both been used, with area reserved for the larger foci. However, while area is used for large macroscopic lesions, it typically is no longer routinely used for microscopic lesions. Foci or focus are now commonly used to refer to a cluster of hepatocytes with tinctorial properties that are different from their neighbors. Foci of cellular alteration have been identified as clear cell, vacuolated, eosinophilic, ground glass, basophilic, tigroid, and mixed and at times have been referred to as hyperplastic foci. Besides tinctorial characteristics, foci can also be differentiated based on histochemical or immunohistochemical reactions or labeling (Beer and Pitot, 1987; Eustis et al., 1990). In general, foci of altered cells are considered preneoplastic lesions although they are not themselves tumors. Currently, most pathologists identify four different types of foci including clear cell, acidophilic, basophilic, and mixed (Maronpot et al.,

1987). As described above, the term hyperplasia is currently only used for nonneoplastic regenerative proliferative lesions and not in association with foci. This change in terminology has resulted in liver alterations that may have been called neoplastic nodules in a previous decade to currently be described as foci.

Summary

In summary, while it seems intuitive that one would evaluate all the pathology data of a chemical to characterize the potential risk of exposure to a xenobiotic, in practice this does not always happen. When assessing the potential for a chemical to cause harm to humans one must remember to examine the entire pathology database in context of the study design, the mode of action of the chemical of concern, and to use the most current interpretation of a lesion to decide on the significance to human health of a particular tissue response.

Acknowledgments

The authors would like to thank Drs. Anna Lowit and Mary Ko Manibusan for helpful review. The opinions in this paper are the authors' and do not reflect the views or policies of the USEPA.

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for acute oral toxicity: HOECHST Aktiengesellschaft, Pharma Forschung, Toxikologie, _Akute *Orale Toxizitat von Phosphor Rot an Weiblichen SPF-Wistar Reatten*, Study Report 131/75, 1975

Exp Key Acute toxicity: oral.001

Administrative Data

Purpose flag: key study
Study result type: experimental result
Reliability: 2 (reliable with restrictions)
Rationale for reliability incl. Deficiencies: Well performed guideline conform non GLP study.

Data source

Reference
Reference: type study report
Year: 1975
Report date: 1975-03-10

Materials and methods

Test type
standard acute method
Limit test
yes
Test guideline
Qualifier according to
Guideline OECD Guideline 401 (Acute Oral Toxicity)
Deviations yes
Principles of method if other than guideline
only one group of animals has been used
a dose of 15000 mg/kg body weight has been used instead of 2000 mg/kg body weight
only female rodents were used because in prior studies sex-related differences had not been noticed
GLP compliance
no study performed before GLP guidelines

Test materials

Identity of test material same as for substance defined in section 1 (if not read-across)
yes
Details on test material
- Name of test material (as cited in study report): Phosphor rot
- Substance type: element
- Physical state: powder
- Stability under test conditions: stable

Test animals

Species
rat
Strain
Wistar
Sex

female
Details on test animals and environmental conditions
TEST ANIMALS
- Source: report 131/75
- Weight at study initiation: see table below
- Fasting period before study: 16 hours
- Housing: in plastic cages on wood shavings
- Diet (e.g. ad libitum): Altromin 1324 (Altrogge)
- Water (e.g. ad libitum): ad libitum

Administration / exposure

Route of administration
oral: gavage
Vehicle
other: 1% starch mucilage
Details on oral exposure
MAXIMUM DOSE VOLUME APPLIED: 15000 mg/kg body weight
Doses
one dose with 15000 mg/kg body weight
No. of animals per sex per dose
10
Control animals
no
Details on study design
- Duration of observation period following administration: 14 days (or other?) 14 days
- Frequency of observations and weighing: 7 days
- Necropsy of survivors performed: yes
- Other examinations performed: clinical signs, body weight,organ weights, histopathology,
other: clinical signs, body weight, necropsy

Results and discussions

Effect levels
Sex female
Endpoint LD50
Effect level > 15000 mg/kg bw
Mortality
no mortality occured during the study
Clinical signs
no clinical signs have been observed
Body weight
92-104 g (average body weight = 96,6 g)
Gross pathology
No effects
Any other information on results incl. tables

body weight of the rats

Animal no.	sex	dose [mg/kg]	initally body weight	body weight after 7 days	body weight after 14 days

1	female	15000	98	138	160
2	female	15000	90	120	136
3	female	15000	102	144	166
4	female	15000	94	128	150
5	female	15000	94	126	150
6	female	15000	92	126	144
7	female	15000	104	146	172
8	female	15000	96	124	142
9	female	15000	96	138	158
10	female	15000	100	128	144

Applicant's summary and conclusion

Interpretation of results
practically nontoxic
Criteria used for interpretation of results
EU
Conclusions
The LD50 (acute oral) of red phoshorus in female rats is > 15000 mg/kg bw.

Executive summary

After the administration of the highest applicable amount of 15,000 mg red phosphorus

/kg bw, the all animals survived and showed normal behavior during the 14 days observation time.

The trend in body weight of the animals during the observation period is given in the table above. The necropsy of the killed animals at the end of the observation period did not reveal any macroscopically visible changes.

Based on the current results the specific acute oral toxicity could not be determined. The acute oral LD50 for female rats is for sure above 15000 mg/kg body weight.

Annex II: Robust Study Summaries presented within the REACH Registration dossier for acute oral toxicity: Henry, M.C., J.J. Barkley, and C.D. Rowlett.. *Mammalian Toxicological Evaluation of hexachloroethane Smoke Mixture and Red Phosphorus*. Final Report. AD-A109593.

Endpoint study record: Sup_1981_Litton Bionetics_DAMD7-78-C-8086

UUID	IUC5-cb7a990a-ca57-4cd7-b5b1-5045525f2b09
Dossier UUID	IUC5-4043795a-880e-45c0-bf0c-16b88108ae8e
Author	XML Transformation V1.0 Plug-In
Date	2010-02-02 11:39:24 CET
Remarks	Successfully migrated to IUCLID 5.2 format.

Administrative Data

[]

Purpose flag	supporting study; robust study summary
Data waiving	
Justification for data waiving	
Study result type	experimental result **Study period** 1981
Reliability	3 (not reliable)
Rationale for reliability incl. deficiencies	non GLP study

Data source

Reference

Reference type	Author	Year	Title	Bibliographic source	Testing laboratory	Report no.	Owner company	Company study no.	Re d
study report	Mary C. Henry, Jesse J. Barkley, Jr., C. David Rowlett	1981	MAMMALIAN TOXICOLOGY EVALUATION OF HEXACHLORETHANE SMOKE MIXTURES AND RED PHOSPHORUS		Litton Bionetics, Inc. 5516 Nicholson Lane, Kensington, MD 20795	DAMD7-78-C-8086	US Army Medical research And Development Command		

Data access

other: approved for public release; distribution unlimited

Data protection claimed

Cross-reference to same study

not applicable

Materials and methods

Test type

fixed dose procedure

Limit test

yes

Test guideline

Qualifier	Guideline	Deviations
no guideline followed		

Principles of method if other than guideline

Male and female Fischer 344 (F344) albino rats were obtained from Charles River Breeding Laboratories, Inc. Portage, Michigan, Animals were acclimated to laboratory conditions for 1 week, They were Individually housed In wire- bottom cages, In quarters maintained at temperatures of 72° to 76°F and 39 to 54 percent relative humidity, A 12-hour light cycle was maintained with artificial illumination. Acidified water (pH 2.5) and Purina Rat Chow were provided ad libitum except 18 to 24 hr before treatment when food was withheld. The oiled HP was suspended in corn oil and administered by oral Intuba-tion at concentration levels to provide 1.0 mL per 100 g body weight. Animals were identified by ear tags. Male rats weighing between 190 and 240 g and female rats with body weights of 146 to 172 g, 10 to 13 weeks of age were used in the range-finding studies. These studies were performed with two males and two females at each of four dose levels. Three additional male and three female rats were administered the high-dose level 6 days after the first experiment. To confirm the results of the second treatment with the high-dosage level, an additional 10 male (184 to 210 g body weight) and 10 female (163 to 174 g body weight) rats, 9 to 13 weeks of age, were given this dose. Animals were observed for 14 days following treatment.

GLP compliance

no

Test materials

Identity of test material same as for substance defined in section 1 (if not read-across)

yes

Test material identity

Identifier	Identity
Common name	Red Phosphorus
CAS number	7723-14-0

Details on test material

- Name of test material (as cited in study report): oiled red phosphorus Albright and Wilson, LDT. Lot LT 22 RED PHOSPHORUS)
- Substance type: element
- Physical state: solid / powder
- Analytical purity: > 94,6 % +- 1,20 %
- Impurities (identity and concentrations): < 0,0055 % +- 0,0020 % yellow phosphorus
- Composition of test material, percentage of components:approx. 94,6 % total phosphorus, 0,08 % +- 0,010 % mineral oil

Confidential details on test material

Test animals

Species

rat

Strain

Fischer 344

Sex

male/female

Details on test animals and environmental conditions

EST ANIMALS
- Source: study report
- Age at study initiation: 10 week old
- Weight at study initiation: unknown
- Housing: wired bottom cages
- Diet (e.g. ad libitum): Purina Rat Chow
- Water (e.g. ad libitum): Acified water (pH 2.5)
- Acclimation period: 1 week

ENVIRONMENTAL CONDITIONS
- Temperature (°F): 72° to 76°F
- Humidity (%): 39 to 54 percent relative humidit
- Air changes (per hr): unknown
- Photoperiod (hrs dark / hrs light): 12h dark / 12h with artificial illumination.

Administration / exposure

Route of administration

oral: gavage

Vehicle

corn oil

Details on oral exposure

Doses

1000, 3160 and 6810 mg/kg

No. of animals per sex per dose

Control animals

no

Details on study design

Statistics

Any other information on materials and methods incl. tables

Results and discussions

Preliminary study (if fixed dose study)

Effect levels

Sex	Endpoint	Effect level	Based on	95% CL	Remarks
male/female	LD50	> 2000 mg/kg bw			

Mortality

Clinical signs

Body weight

Gross pathology

Other findings

Any other information on results incl. tables

T Days after Treatmenthe results of the range-finding study, employing two rats per sex per dose, sugg
Oral administration of the high dose to an additional 10 rats per sex, did not produce as marked a toxic e

Table 8:

Dose (mg/kg)	Mean Body Weight (g)
	Days after Treatment
	0
Males	
1,000	204
3,160	199
6,810	211
10,000	220
10,000	203
Females	
1,000	154
3,160	151
6,910	156
10,000	162
10,000	166

Overall remarks, attachments

Overall remarks

Applicant's summary and conclusion

Interpretation of results

practically nontoxic

Criteria used for interpretation of results

not specified

Conclusions

LD 50 > 2000 mg/kg body weight

Executive summary

Gastric Intubation of 1,000, 3,610, and 6,810 mg/kg did not produce lethality, After administration of 1

(13) LEVEL

AD A109593

MAMMALIAN TOXICOLOGIC EVALUATION OF HEXACHLOROETHANE SMOKE MIXTURE AND RED PHOSPHORUS

Final Report

Prepared by

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September 1981

Supported by

US ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND
Fort Detrick, Frederick, MD 21701

Contract DAMD 17-78-C-8086

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5516 Nicholson Lane
Kensington, MD 20795

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JAN 13 1982
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The findings in this report are not to be construed as an official Department of the Army position unless so designated by other authorized documents.

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EXECUTIVE SUMMARY

The objectives of this program are to provide confirmation of the organic combustion products from burning of a hexachloroethane (HC) smoke mixture and to define the acute toxicologic effects of uncombusted red phosphorus (RP) to mammalian systems. The toxicologic evaluation of RP was initiated in response to the proposed establishment by the US Army of an RP onshore production facility. Chemical analyses of four red phosphorus samples, three samples of which contained light lubricating or mineral oil showed that all samples did not meet the complete list of specifications. The total phosphorus content was below the specified 98.75 percent. The oil content was either above or below the required 1.25 percent. None of the samples met the criteria for particle size and the oiled samples had a tendency to agglomerate. All samples contained less white phosphorus than the allowed maximum of <0.01 percent.

Attempts to produce an aerosol in an inhalation chamber were unsuccessful. An aerosol of oiled red phosphorus could not be sustained with a fluid bed generator, Laskin aerosol system, or a Wright Dust Feed mechanism. The dust feed was able to generate a low chamber concentration but jammed frequently due to the clumping of the oiled material. The majority of the oiled red phosphorus would not pass through a sieve which excludes particles above 150 micrometers Less than 0.5 percent of the material passed through a sieve with a 38 micrometers cutoff. These studies indicated that the oiled red phosphorus contains very few respirable particles and would not be a potential industrial inhalation hazard.

Gastric intubation of 1,000, 3,610, and 6,810 mg/kg did not produce lethality. After administration of 10,000 mg/kg to five Fischer 344 rats per sex, one male rat died within 24 hours. This experiment was repeated using 10 rats per sex and one female died 7 days after treatment. This animal gave signs of an infection. Other toxic signs at the high-dose level were failure to gain body weight or dose of weight during the 14-day observation period.

The oiled red phosphorus did not elicit an irritation response when applied as a 0.5 g dose on intact or abraded rabbit skin. The instillation of 100 mg of the test material into rabbit eyes did not produce any irritation or injury. Intradermal injection into guinea pigs produced signs of irritation but not skin sensitization. Application of the test material to guinea pig skin did not result in irritation or sensitization responses.

Sampling of the gas phase from a burn of the hexachloroethane smoke mixture (zinc oxide and aluminum) showed the presence of phosgene, tetrachloroethylene, carbon tetrachloride, hexachloroethane, and hexachloro-1,3-butadiene.

RED PHOSPHORUS AEROSOLIZATION

Generation of an oiled red phosphorus aerosol for inhalation exposures could not be accomplished. An aerosol of the material could not be sustained with a fluid bed generator, Laskin aerosol system or a Wright Dust Feed mechanism. The dust feed was able to generate a low chamber concentration but jammed frequently due to the clumping of the oiled material. Two samples were taken with an Anderson 2000 Cascade Impactor to determine particle size distribution (Tables 6 and 7).

The jamming of the Wright Dust Feed was due in part to large particles bridging and blocking smaller particles. The oiled RP was sieved in a series of stainless steel NMB sieves. The majority of the material would not pass through a 100-mesh sieve which excludes particles above 150 microns. Less than 0.5 percent of the RP passed through a 400-mesh sieve with a 38-micron cutoff. These studies indicated that the oiled RP contained very few respirable particles and work on generation of inhalation chamber aerosols was terminated.

ACUTE MAMMALIAN TOXICITY

Oral Toxicity

The results of the range-finding study, employing two rats per sex per dose, suggested that oiled RP did not produce lethality at doses of 1,000, 3,160, and 6,810 mg/kg (Table 8). Rats of both sexes gained body weight during the 14-day observation period. Intubation of 10,000 mg/kg RP to five rats per sex produced lethality in one male rat. Necropsy findings were gas-filled distended intestines. Although no additional deaths were observed in these groups, the body weights of one male and one female at the end of the observation period were lower than their body weights before treatment. Another female lost body weight between days 7 and 14.

Oral administration of the high dose to an additional 10 rats per sex, did not produce as marked a toxic effect on body weight although some rats of both sex did not gain weight between days 7 and 14. This reduced body weight gain was most apparent in females. The one female which died on day 7 may have had an infection. The lungs were dark red and fluid-filled, and the rat had shown dyspnea.

Skin Irritation Study

Application of 0.5 g of oiled RP to intact and abraded skin for 24 hours did not produce signs of irritation (Table 9). The primary irritation score was 0.2 which indicates that the test material does not have irritation potential. Clinical signs indicative of systemic toxicity were not observed during the course of this study.

Annex III: Vrednie chemichescie veshestva. Neorganicheskie soedinenia elementov V-VII groopp" (Hazardous substances. Inorganic substances containing V-VII group elements), by Bandman A.L. et al., Chimia, 1989

ВРЕДНЫЕ ХИМИЧЕСКИЕ ВЕЩЕСТВА

НЕОРГАНИЧЕСКИЕ СОЕДИНЕНИЯ ЭЛЕМЕНТОВ V-VIII ГРУПП

СПРАВОЧНИК

Под общей редакцией
д-ра биол. наук проф. В. А. Филова

Согласовано с Государственной службой стандартных справочных данных

ЛЕНИНГРАД „ХИМИЯ"
ЛЕНИНГРАДСКОЕ ОТДЕЛЕНИЕ
1989

Органолептические свойства воды меняются только при концентрациях Ф. 0,1—0,5 мг/л.

Гидробионты. Действует на жабры, печень, нервную систему, скелет, чешую. У сельди и некоторых других обитателей моря вызывает гемолиз. Ф. жирорастворим и аккумулируется в тканях, богатых липидами. Фактор биоконцентрации Ф. для лососевых и трески 10^3 — 10^4. Состояние равновесия достигается в течение часов. При содержании в течение 96 ч в воде для омара $ЛК_{50}$ = 200 мкг/л; для креветки 32; для сельди 3,7; для трески 2,8—6,5; для форели 22; для лосося 16 мкг/л (Addison). Порог летального действия Ф. ниже 1 мкг/л для многих видов гидробионтов.

Острое отравление. **Животные.** При кормлении для мышей и крыс $ЛД_{50}$ = 11,5 мг/кг (Красовский и др.), для кроликов 0,21 г (в масле), для кошки 10—30 мг, для собаки 50—100 мг. При вдыхании 0,15—0,16 мг/л паров Ф. мыши, крысы и кролики погибали. Отмечено удлинение систолы, увеличение содержания жира и воды в мозге, сердце, печени, почках и стойкое увеличение содержания пировиноградной кислоты в крови.

Человек — см. [8, с. 128].

Повторное отравление. **Животные.** Крысы погибают после 10—20 в/желудочных введений дозы 0,5 мг/кг (Красовский и др.). При дозах 0,004—0,1 мг/кг все животные переживают 30-дневное введение, но при этом изменяются общее состояние, масса тела, содержание SH-групп, активность щелочной фосфатазы, альдолазы и холинэстеразы крови; $ЕД_{50}$ = 0,05 мг/кг. Ф. обладает кумулятивными свойствами и оказывает гонадотоксическое действие ($ЕД_{50}$ = 0,06 мг/кг). Стрелюхина вводила крысам внутрь Ф. в дозе 1 мг/кг пятикратно. В печени полнокровие, отек, диапедезные кровоизлияния, мелкокапельная жировая дистрофия гепатоцитов и токсический гепатит. У части крыс через 3—4 мес. развивались фиброз и мелкоузелковая форма цирроза печени. Нарушения кровообращения выражены в сроки до 1—2 мес., за 3—4 мес. эти нарушения в значительной степени нормализуются. Во все сроки снижено содержание гликогена; суммарный белок снижен через 15 суток — 2 мес., а через 3—4 мес. повышен.

Установлено снижение активности ферментов антиоксидантной системы кроликов при ежедневном подкожном введении 0,2 % масляного раствора Ф. из расчета 0,5 мг/кг (Шарманов и др.).

Хроническое отравление. **Животные.** Общую картину отравления см. [8, с. 128].

У крыс, содержавшихся в условиях производства Ф. по 4 ч в день до 4 мес., в ряде случаев отмечены экзофтальм, гиперкератоз век; паралич задних конечностей; гнойно-некротические

поражения нижних челюстей (Рузуддинов). Установлена возможность развития хронических воспалительных изменений в слизистой оболочке ротовой полости и других мягких тканей крыс.

При 6-месячном введении Ф. крысам-самцам в желудок в дозе $5 \cdot 10^{-4}$ мг/кг отмечено изменение условнорефлекторной деятельности, содержания SH-групп и β-липопротеидов в сыворотке крови, активности холинэстеразы и альдолазы в крови (Красовский и др.). Два первых показателя изменялись и при дозе $5 \cdot 10^{-5}$ мг/кг. Доза $5 \cdot 10^{-6}$ мг/кг изменений не вызывала.

Ф. обладает мутагенной активностью: в дозах $5 \cdot 10^{-4}$ — $5 \cdot 10^{-5}$ мг/кг вызывает снижение митотического индекса, увеличение числа хромосомных аберраций и аберрантных клеток. В тех же дозах показано его гонадотоксическое действие — морфологические изменения в семенниках крыс. В дозе $5 \cdot 10^{-4}$ мг/кг нарушает репродуктивную функцию крыс-самок, влияя на развитие эмбрионов.

Человек. Наиболее типичны изменения в костях, особенно омертвение челюстей. Процесс начинается иногда сильной зубной болью, обычно в кариозных зубах, или воспалением надкостницы около кариозного зуба. Иногда разрушение и выпадение зубов происходят безболезненно. Если зуб удален, заживление идет медленно. Образуются гнойные свищи, вскрывающиеся обычно в рот, если поражена верхняя челюсть, и наружу при заболевании нижней челюсти. Кроме гноя через свищи отделяются и кусочки кости. Запах от больного нестерпим для окружающих. Заболевание может вызвать потерю аппетита, анемию, истощение, лихорадку. В части случаев — исход смертельный; при выздоровлении лицо остается обезображенным. Иногда омертвение и нагноение распространяются на кости орбиты и ведут к потере глаза либо вызывают менингит со смертельным исходом. У лиц со здоровыми зубами Ф. не вызывает появления очагов омертвения кости даже при работе в течение 10—20 лет; при наличии кариозных зубов заболевание может начаться через 10—12 мес. [8, с. 128—129]. У лиц, перенесших омертвение челюстей, через 1—1,5 года после операции могут вновь появиться головные боли, боли в зубах и челюстях без видимых поражений в них. Заболевания развиваются обычно после нескольких лет работы с Ф., хотя известен случай хронического отравления после 7-недельной работы. Иногда омертвение челюстей развивается через несколько лет после прекращения работы с Ф.

Изменения других костей выражаются главным образом в утолщении и разрыхлении надкостницы, уплотнении самой кости. Рано появляются эпифизарные полосы, просветление костей, резкие краевые контуры их. Изменения носят фазный

English rough translation:

Acute poisoning. Animals. When *kormleini* mouse and rat LD50 = 11.5 mg / kg (Krasoysky, etc.), for rabbits 0.21 g (in oil), Cat 10-30 mg for dogs 50-100 mg. If inhaled 0,15-0,16 mg / l vapor F. mice, rats and blood *pogigbali* faces. Marked prolongation of systole, increased con Jania fat and water in the brain, heart, *iechepi*, kidneys, and persistent pirovinogradpoy increase in acid in the blood.

Krasovskid GN et al / / Hygiene and sanitation. 1979. N4 5. Pp. 74-75.

according to	other guideline: FDA, 16 CFR 1500.41 91 26,141	no

Principles of method if other than guideline

GLP compliance

no

Identity of test material same as for substance defined in section 1 (if not read-across)

yes

Test materials

Test material identity

Identifier	Identity
Common name	red phosphorus
CAS number	7723-14-0

Details on test material

- Name of test material (as cited in study report): oiled red phosphorus Albright and Wilson, LDT. Lot LT 22 RED PHOSPHORUS)
- Substance type: element
- Physical state: solid / powder
- Analytical purity: > 94,6 % +- 1,20 %
- Impurities (identity and concentrations): < 0,0055 % +- 0,0020 % yellow phosphorus
- Composition of test material, percentage of components:approx. 94,6 % total phosphorus, 0,08 % +- 0,010 % mineral oil

Confidential details on test material

Test animals

Species

rabbit

Strain

New Zealand White

Details on test animals and environmental conditions

TEST ANIMALS
- Source: study report
- Age at study initiation: 10 week old
- Weight at study initiation: unknown
- Housing: wired bottom cages
- Diet (e.g. ad libitum): Purina Rat Chow
- Water (e.g. ad libitum): Acified water (pH 2.5)
- Acclimation period: 1 week

ENVIRONMENTAL CONDITIONS
- Temperature (°F): 72° to 76°F
- Humidity (%): 39 to 54 percent relative humidit
- Air changes (per hr): unknown
- Photoperiod (hrs dark / hrs light): 12h dark / 12h with artificial illumination.

Test system

Type of coverage

occlusive

Preparation of test site

abraded

Vehicle

other: sterile isotonic saline solution

Amount/concentration applied

0.5 g of red phosphorus was mixed with 0,5 ml sterile isotonic saline solution

Duration of treatment / exposure

24 hours

Observation period

72 hours

Number of animals

six

Control animals

no

Details on study design

TEST SITE
- Area of exposure: 1 inch square
- % coverage: unknown
- Type of wrap if used: plastic

REMOVAL OF TEST SUBSTANCE
- Washing (if done): no washing done
- Time after start of exposure:24 hours

SCORING SYSTEM: see table below

Any other information on materials and methods incl. tables

Erythema and Eschar Formation	Value	Edema Formation
no erythema	0	No edema
very slight erythema (barely percentible)	1	very slight edema (b
well defined erythema	2	well defined edema
moderate to severe erythema	3	moderate edema (r
severe erythema (beet redness) to slight eschar formation (injuries in dpth)	4	sever edeme (raised

Results and discussions

Irritation / corrosion results

Irritation parameter	Basis	Time point	Score	Max. score	Reversibility	Remarks
primary dermal irritation index (PDII)	mean			0.2	no data	the test material does not have irritation potential

Irritant/corrosive response data

the test material does not have irritation potential

Other effects

Clinical signs indicative of systemic toxicity were not observed during the course of this study.

Any other information on results incl. tables

	Erythema and Eschar Formation				Edema Formation			
Rabbit	Intact Skin		Abraded Skin		Intact Skin		Abraded Skin	
number	24hr	72hr	24hr	72hr	24hr	72hr	24hr	72hr
2354D	0	0	1	0	0	0	1	0
2355D	0	0	1	0	0	0	1	0
2356D	0	0	1	0	0	0	0	0
2357D	0	0	1	0	0	0	0	0
2358D	0	0	1	0	0	0	0	0
2359D	0	0	1	0	0	0	0	0

Overall remarks, attachments

Overall remarks

Applicant's summary and conclusion

Interpretation of results

not irritating

Criteria used for interpretation of results

expert judgment

Conclusions

the test material does not have irritation potential

Executive summary

Application of 0,5 g of oiled RP to intact and abraded skin for 24 hours did not producte signs of irritatic

Cross-reference to other study

Exp Supporting Skin irritation / corrosion.002

Administrative Data

Purpose flag supporting study
Study result type experimental result
Study period 1975
Reliability 3 (not reliable)
Rationale for reliability incl. deficiencies The study has been carried out with a 10 % dilution of red phosphorus

Data source

Reference
Reference type study report
Year 1981
Report date 1975-03-10

Materials and methods

Type of method
in vivo
Test guideline
Qualifier no guideline followed
Principles of method if other than guideline
Patch-Test:
10% Red Phosphorus/starch mucilage suspension was applied to clipped skin of 6 russian rabbits for 24 h. The trunk of the animals was wrapped with an occlusive plastic. The skin sites were graded for irritation and edema using the Draize scoring system. The application was repeated daily on 5 consecutive days.
GLP compliance
no study performed before GLP guidelines
Identity of test material same as for substance defined in section 1 (if not read-across)
yes

Test animals

Species
rabbit
Strain
other: Albino - Russia
Details on test animals and environmental conditions
no data

Test system

Type of coverage
occlusive
Preparation of test site
shaved

Vehicle
water
Amount/concentration applied
0,5 ml Red Phsophorus (10% in starch mucilage)
Duration of treatment / exposure
24 hours
Observation period
immediately after removal of the dressing, 24, 48 and 72 hours after exposure
Number of animals
6
Control animals
no
Details on study design
Versuchsdurchführung:
Die Flankenhaut von 6 Kaninchen im Gewicht von 1,5 - 2,0 kg wurde mit einer elektrischen Haarschneidemaschine an zwei nebeneinanderliegenden Stellen auf einer Fläche von je 3 x 3 cm enthaart* Jeweils eine der geschorenen. Hautstellen wurde zusätzlich mittels eines Schröpfschneppers skarifiziert. 2,5 x 2,5 cm große Läppchen aus chirurgischer Gaze wurden mit 0,5 ml einer 10% igen Suspension des, Präparates getränkt und mittels eines Klebestreifens auf die vorbereiteten Hautstellen geklebt. Durch eine indifferente, undurchlässige, 6-8 cm breite PVC "Folie wurden die Läppchen abgedeckt und anschließend der Rumpf der Tiere mit einer elastischen Dauerbinde umwickelt. Die Einwirkungszeit betrug 24 Stunden. Eine Befunderhebung erfolgte unmittelbar nach Abnahme des Verbandes (24~Stunden-Wert) sowie 48 und 72 Stunden nach Versuchsbeginn.

Results and discussions

Irritation / corrosion results
Irritation parameter overall irritation score
Basis mean
Time point 24h
Score 0.4
Max. score 4
Reversibility fully reversible within: 48h
Any other information on results incl. tables

Ergebnis:

Die Applikation der 10%igen Suspension führte nach 24 Stunden bei 5 Tieren an der intakten Flankenhaut zu einem sehr leichten kaum wahrnehmbaren Erythem. An der skarifizierten Flankenhaut war bei allen Tieren ein sehr leichtes bis gut ausgeprägtes Erythem, bei 5 Tieren ein leichtes Ödem zu beobachten. Nach 48 Stunden zeigte die intakte Flankenhaut aller Kaninchen keine Symptome mehr, die skarifizierte Flankenhaut zeigte ein sehr leichtes bis gut ausgeprägtes Erythem. Außerdem wurde an 5 Tieren ein sehr leichtes, kaum wahrnehmbares Ödem beobachtet. Nach 72 Stunden konnte an der skarifizierien Flankenhaut von 5 Tieren ein sehr leichtes Erythem festgestellt werden (Index: 1,25). Die Auswertung und Einzelbefunde sind den Anlagen 1 und 2 zu entnehmen,

Anlage 2:

Tier	Hautreaktion 24 nach	48 nach	72 Std.	96 Std.	Summe 24+72

Nr.		Appl. intakt	Appl. skarif	Appl. intakt	Appl. skarif	nach. Appl. intakt	nach. Appl. skarif	nach. Appl. intakt	nach. Appl. skarif	Std. (l +2 + 5 +6)
		1	2	3	4	5	6	7	8	
67	Erythem	1	1	0	2	0	1			3
	Oedem	0	0	0	1	0	0			
68	Erythem	1	2	0	2	0	1			6
	Oedem	0	2	0	1	0	0			
69	Erythem	0	1	0	1	0	0			3
	Oedem	0	2	0	0	0	0			
70	Erythem	1	2	0	2	0	1 .			6
	Oedem	0	2	0	1	0	0 .			
71	Erythem	1	2	0	2	0	1			6
	Oedem	0	2	0	1	0	0			
72	Erythem	1	2	0	2	0	1			6
	Oedem	0	2	0	1	0	0			

Applicant's summary and conclusion

Interpretation of results
not irritating
Criteria used for interpretation of results
EU

Conclusions
10% Red Phosphorus in starch mucilage was not irritant to rabbits skin neither after a single 24h exposure nor after repeated exposure (5 times on 5 consecutive days).
Executive summary

10% Red Phosphorus/starch mucilage suspension was applied to clipped skin of 6 russian rabbits for 24 h. The trunk of the animals was wrapped with an occlusive plastic. The skin sites were graded for irritation and edema using the Draize scoring system. The application was repeated daily on 5 consecutive days.

The substance was not irritant to rabbits skin neither after a single 24h exposure nor after repeated exposure (5 times on 5 consecutive days).

Annex V: ISRIM: evaluation of the acidity and conductivity of the smoke generated burning a polyamide resin containing Red Phosphorus Flame Retardant according to CEI EN 50267-2-2: 1999 and CEI EN 50267-1: 1999

ISRIM
ISTITUTO SUPERIORE DI RICERCA E FORMAZIONE
SUI MATERIALI SPECIALI PER TECNOLOGIE AVANZATE

ISRIM Società Consortile a r.l.
05100 Terni Strada di Pentima 4
Tel. 0744 - 547801
Fax. 0744 - 470174

TEST REPORT

Customer: **Italmatch Chemicals S.p.A.**

Reference Standards:

CEI EN 50267-2-2: 1999 — Part 2-2: Procedures – Determination of degree of acidity of gases for materials by measuring pH and conductivity

CEI EN 50267-1:1999 — Common test methods for cables under fire condition – Test on gases evolved during combustion of material from cables
Part 1: Apparatus

Test condition:

Test temperature: > 935°C

Air supply system: Method 3 (CEI EN 50267-1): the mixture of air and combustion gas is sucked by a pump

Flow rate of air: 30 l/min

Specimen weight: 1000 mg ± 5 mg

Test Requirements:

pH > 4,3

conductivity < 10 µS/mm

Samples:

Materials	**Formulation 1**	**Formulation 2**
PA6,6 GF30% (Latamid 66 G/30)	87%	100%
Masteret 20450B2	13%	--

Results:

	Formulation 1	**Formulation 2**
pH	**7,3**	**8,3**
conductivity (µS/mm)	**6,9**	**12,3**

NOTES:
In agreement with the customer, it was carried out only one test determination on each sample

Terni, 28th September 2012

Fire Testing Laboratory Head
(Vincenza Morone)
Vincenza Morone

Final report

Flame Retardant Emissions in the Life Cycle of Plastic Compounds (FLeK)

For:
BASF SE
Herr Dr. Axel Ebenau
E-KTE/IE – F206.
67056 Ludwigshafen

Conducted by:
Fraunhofer-Institut für Umwelt-, Sicherheits und Energietechnik UMSICHT
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3 Investigated materials

The basic composition of the investigated materials is shown in table 3-1. Materials were provided by the customer as granules which then were molded into adequate test specimens.

Table 3-1: examined compounds

#	Designation	Components	Amount
#1	Ultramid® A3X2G5 PA66-GF25-FR (52) Red P	Polyamid PA66	68-77 %
		Glass fibres	25%
		Red phosphorus	6-7%
#2	PA66-GF25-FR Org. P compound	Polyamid PA66	55%
		Glass fibres	25%
		Exolit OP 1312	20%
#3	PA66-GF25-FR (17) halogenated	Polyamid PA66	55%
		Glass fibres	25%
		Saytex HP 3010 (brom. Poystyrol)	20%
#4	PA66-GF30-FR (17) halogenated	Polyamid PA66	o. A.*
		Glass fibres	30%
		FR	o.A.*
#5	PA66-GF25-FR (52) Red P	Polyamid PA66	o.A.*
		Glass fibres	25%
		Red phosphorus	o.A.*
#6	PA66-GF25-FR (52) Red P	Polyamid PA66	>57%
		Glass fibres	25%
		Red phosphorus	<15%

* o.A. no information available

7 Emissions in case of fire

7.1 Test method of fire

The fire testing, heat release measurements and smoke density / toxicity have been commissioned by Fraunhofer UMSICHT to Currenta GmbH & Co OHG.

The investigations were carried out in line with the European Railway standard CEN/TS 45545-2.

The study was conducted with the six materials described in table 1-1 Including Ultramid® A3X2G5.

The tests were conducted at specimens that were horizontally positioned within the test chamber and thermally stressed with an heat emitter with a power of 25 kW/m². The combustion gases were collected within the chamber for a period of 20 minutes. The optical density of the smoke gas was measured with a light beam, the toxicity of the flue gases after 4, 8, 12 and 20 min was determined by infrared spectroscopy and subsequent calculation of the CIT (conventional index of toxicity).

$$CIT = 0{,}0805 \cdot \sum_{i=1}^{8} \frac{c_i}{C_i}$$

c_i concentration of the i^{th} component of flue gas in the Chamber
C_i reference concentration of the ith component of flue gas, see table 7-1

Table 7-1: Reference concentration of gas components with acute inhalation toxicity

Flue gas component	Reference concentration in mg/m³
Carbon dioxide CO_2	72000
Carbon monoxide CO	1380
Hydrogen fluoride HF	25
Hydrogen chloride HCl	75
Hydrogen bromide HBr	99
Hydrogen cyanide HCN	55
Nitrogen oxides NOX	38
Sulphur dioxide SO_2	262

Table 7-2: Smoke density and CIT limits acc. to EN ISO 5659-2

EN ISO 565-2	HL 1	HL 2	HL 3
Ds(max) (flue gas density)	600	300	150
CIT after 4 or 8 min (max)	1,2	0,9	0,75

In addition to the 8 gas components fixed in EN ISO 565-2 PH_3 was determined with the help of test tubes. Test tubes with different sensitivity were used: Draeger tubes 0, 01/a with a range of 0.01-1 ppm and Draeger tubes 25/a with a range of 25-10000 ppm.

7.2 Results fire tests

Table 7-3: Results fire tests

	#1 Ultramid® A3X2G5	#2 PA66 GF25 Org. P compound	#3 PA66 GF25 halogenated	#4 PA66 GF30 halogenated	#4 PA66 GF25 red P (EU)	#6 PA66 GF25 red P (Asia)
Smoke density Ds(max)	188	111	521	345	365	337
Mass loss in %	17,7	22,1	51,2	30,6	32,7	27,2
Time to ignition in s	50	54	46	57	82	79
Time to extinction in s	590	1200	927	480	1167	937

Table 7-4: Results PH_3

	#1 Ultramid® A3X2G5	#2 PA66 GF25 Org. P compound	#3 PA66 GF25 halogenated	#4 PA66 GF30 halogenated	#4 PA66 GF25 red P (EU)	#6 PA66 GF25 red P (Asia)
Phosphin in ppm [9] (Draeger tube)	0,3	< 0,01	1 - 25	1 - 25	1 - 25	1 - 25
	0,6	0,3	1 - 25	1 - 25	1 - 25	1 - 25
	0,3	0,1	1 - 25	1 - 25	1 - 25	1 - 25

9 In the semi-quantitative determination of PH_3 in compounds #2, #4, #5 and #6 using Draeger tubes measuring range of 0.01 to 1 ppm was exceeded. In a second measurement, using Draeger tubes with a measuring range of 25 - 900 ppm no PH_3 could be identified. Therefore, the PH_3 concentration was between 1 and 25 ppm. As compounds #3 and #4 do not contain phosphorus, a cross-sensitivity of Draeger tubes for PH_3 must be assumed.

7.2.1 Ultramid® A3X2G5

Figure 7.1: Ultramid® A3X2G5

Table 7-5: Ultramid® A3X2G5 smoke gas components, CIT

time	CO2 mg/m³	CO mg/m³	HF mg/m³	HCl mg/m³	HBr mg/m³	HCN mg/m³	NO_2 mg/m³	SO_2 mg/m³	CIT
4 min	6219	164	n. d.	n. d.	39	23	n. d.	n. d.	0,08
8 min	8991	211	n. d.	n. d.	37	29	9	n. d.	0,11
12 min	11387	245	n. d.	n. d.	37	31	13	n. d.	0,13
20 min	15305	304	n. d.	n. d.	34	32	66	n. d.	0,25

7.2.2 PA66 GF25 (ord. P compound)

Figure 7.2: PA66 GF25 (ord. P compound)

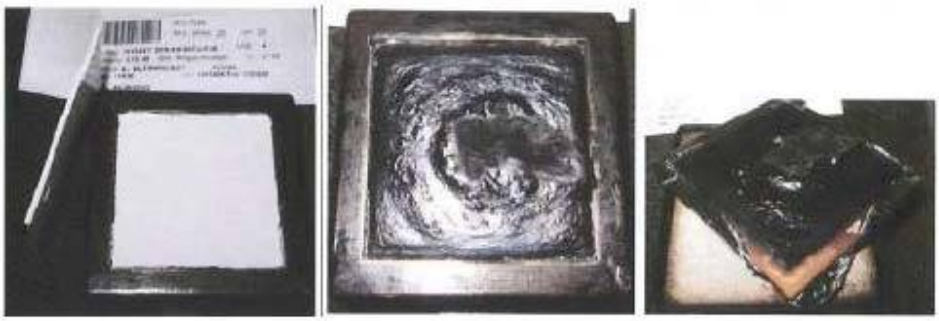


Table 7-6: PA66 GF25 (ord. P compound), smoke gas components, CIT

time	CO2 mg/m³	CO mg/m³	HF mg/m³	HCl mg/m³	HBr mg/m³	HCN mg/m³	NO_2 mg/m³	SO_2 mg/m³	CIT
4 min	3850	12	n. d.	n. d.	n.d.	n.d.	n. d.	n. d.	0,01
8 min	7018	41	n. d.	n. d.	n.d.	n.d.	28	n. d.	0,07
12 min	10775	100	n. d.	n. d.	45	14	71	n. d.	0,23
20 min	15294	169	n. d.	n. d.	38	22	92	n. d.	0,29

7.2.3 PA66 GF25 (halogenated FR)

Figure 7.3: PA66 GF25 (halogenated FR)

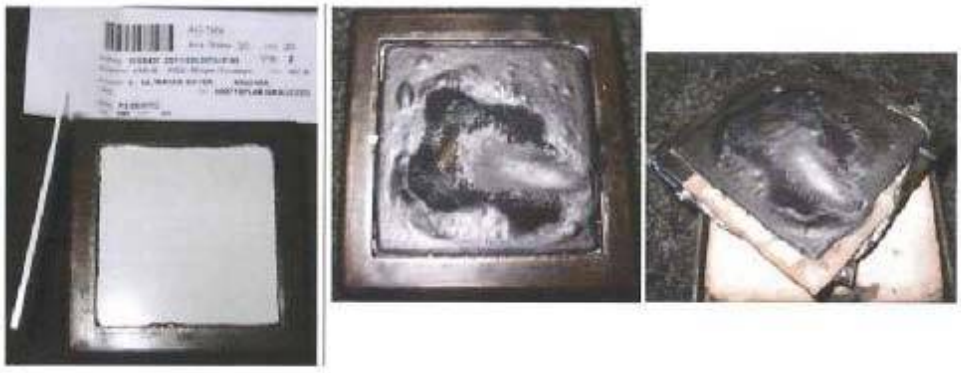


Table 7-7: PA66 GF25 (halogenated FR), smoke gas components, CIT

time	CO2 mg/m³	CO mg/m³	HF mg/m³	HCl mg/m³	HBr mg/m³	HCN mg/m³	NO_2 mg/m³	SO_2 mg/m³	CIT
4 min	4541	856	n. d.	n. d.	78	124	48	27	0,41
8 min	8740	1310	n. d.	n. d.	66	163	81	33	0,56
12 min	12649	1511	n. d.	n. d.	56	168	134	33	0,69
20 min	17226	1734	n. d.	n. d.	54	172	134	26	0,71

7.2.4 PA66 GF30 (halogenated FR)

Figure 7.4: PA66 GF30 (halogenated FR)

Table 7-8: PA66 GF30 (halogenated FR), smoke gas components, CIT

time	CO2 mg/m³	CO mg/m³	HF mg/m³	HCl mg/m³	HBr mg/m³	HCN mg/m³	NO_2 mg/m³	SO_2 mg/m³	CIT
4 min	6566	592	n. d.	n. d.	76	69	53	12	0,32
8 min	10802	803	n. d.	n. d.	59	79	99	10	0,44
12 min	13204	862	n. d.	n. d.	50	79	101	n.d.	0,44
20 min	16784	934	n. d.	n. d.	45	82	111	n.d	0,46

7.2.5 PA66 GF25 (red P) EU

Figure 7.5: PA66 GF25 (red P) EU

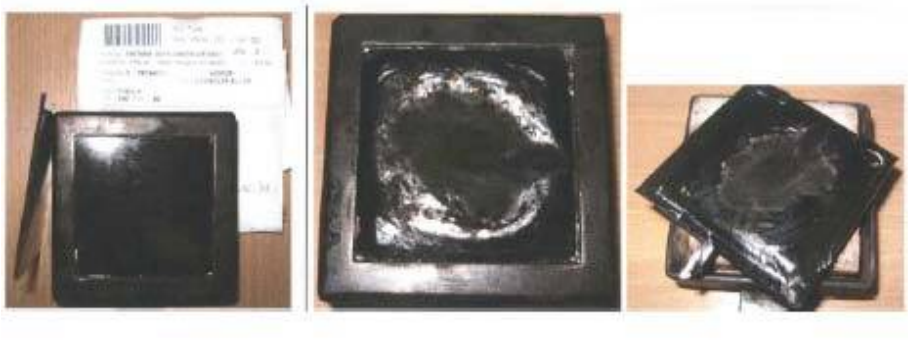


Table 7-9: PA66 GF25 (red P) EU, smoke gas components, CIT

time	CO2 mg/m³	CO mg/m³	HF mg/m³	HCl mg/m³	HBr mg/m³	HCN mg/m³	NO_2 mg/m³	SO_2 mg/m³	CIT
4 min	5070	267	n. d.	n. d.	n.d.	30	14	n.d.	0.10
8 min	10215	384	n. d.	n. d.	n.d.	52	61	n.d.	0,24
12 min	14524	482	n. d.	n. d.	n.d.	61	81	n.d.	0,31
20 min	20576	545	n. d.	n. d.	n.d.	62	107	n.d	0,37

7.2.6 PA66 GF25 (red P) Asia

Figure 7.6: PA66 GF25 (red P) Asia

Table 7-10: PA66 GF25 (red P) EU, smoke gas components, CIT

time	CO2 mg/m³	CO mg/m³	HF mg/m³	HCl mg/m³	HBr mg/m³	HCN mg/m³	NO_2 mg/m³	SO_2 mg/m³	CIT
4 min	5838	287	n. d.	n. d.	n.d.	44	29	n.d.	0,15
8 min	10371	406	n. d.	n. d.	n.d.	59	43	n.d.	0,21
12 min	13791	488	n. d.	n. d.	n.d.	67	58	n.d.	0,26
20 min	19109	544	n. d.	n. d.	n.d.	71	82	n.d	0,33

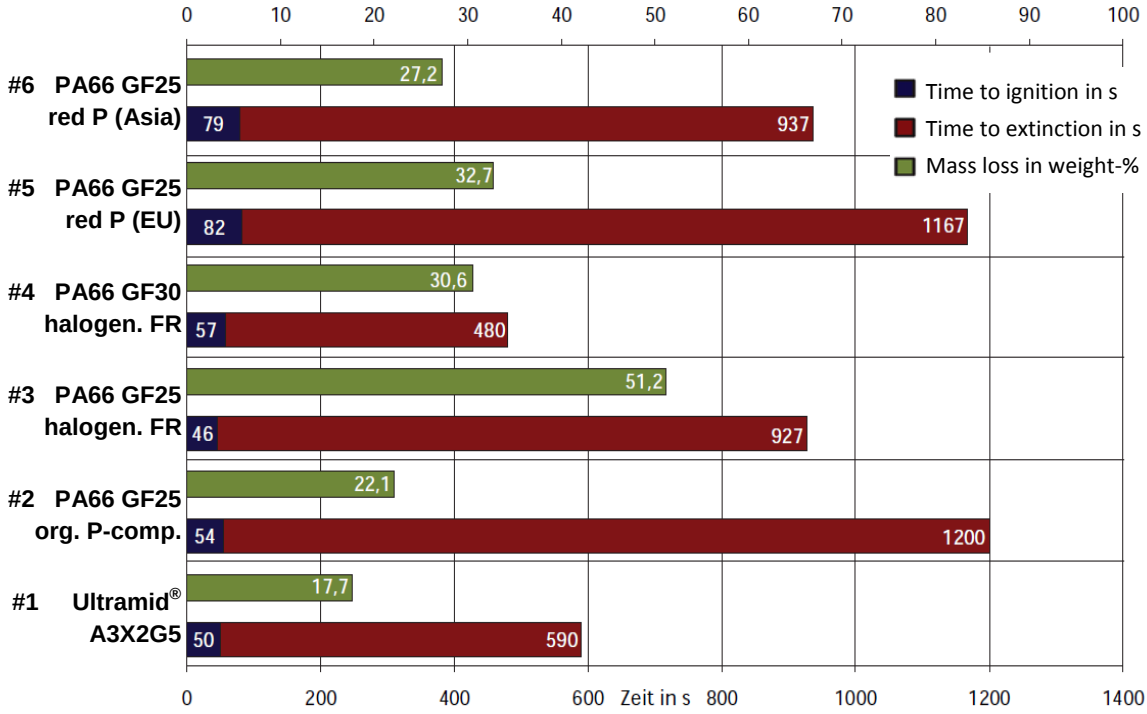
7.3 Conclusion fire tests

The comparison of the six conducted materials showed a great diversity in combustion properties. The ignition times of compounds #3 and #4 (halog. FR), compound #2 (org. P compound) and Ultramid® A3X2G5 were close

to each other (46-57 s), whereas the time to extinction of the materials widely scattered.

Compounds #‘5 and #6 (red P) were ignited much later and showed a relativelyl long burning time. (Figure 7.7)

Figure 7.7: Comparison of burning parameters



Compounds #5 and #6 both ignited over 20 seconds later than the other examined materials. The smoke density and the loss of mass were comparable to compound #4. The value of CIT was in the middle of all examined materials.

Compound #5 (red P) was in mass loss and smoke density comparable to the compound #4, but showed a much longer burning time at similar smoke density and lower CIT.

compound #4 (halogen. FR) had the shortest burning time, but also high mass loss of 30% and and a relatively high CIT value at 4 min measure time compared to Ultramid® A3X2G5. Due to the increased mass loss the smoke density showed also higher values.

compound #3 (halogen. FR) had the highest mass loss with 50% and also the highest smoke density. The CIT value was at 4 min measure time already high and further increased over the course of the measurements.

Compound #2 (org.P compound) had the longest burning time but in relation to that a low mass loss. Despite the long burning time and according to the low mass loss the smoke density also was low. This results in a low CIT value.

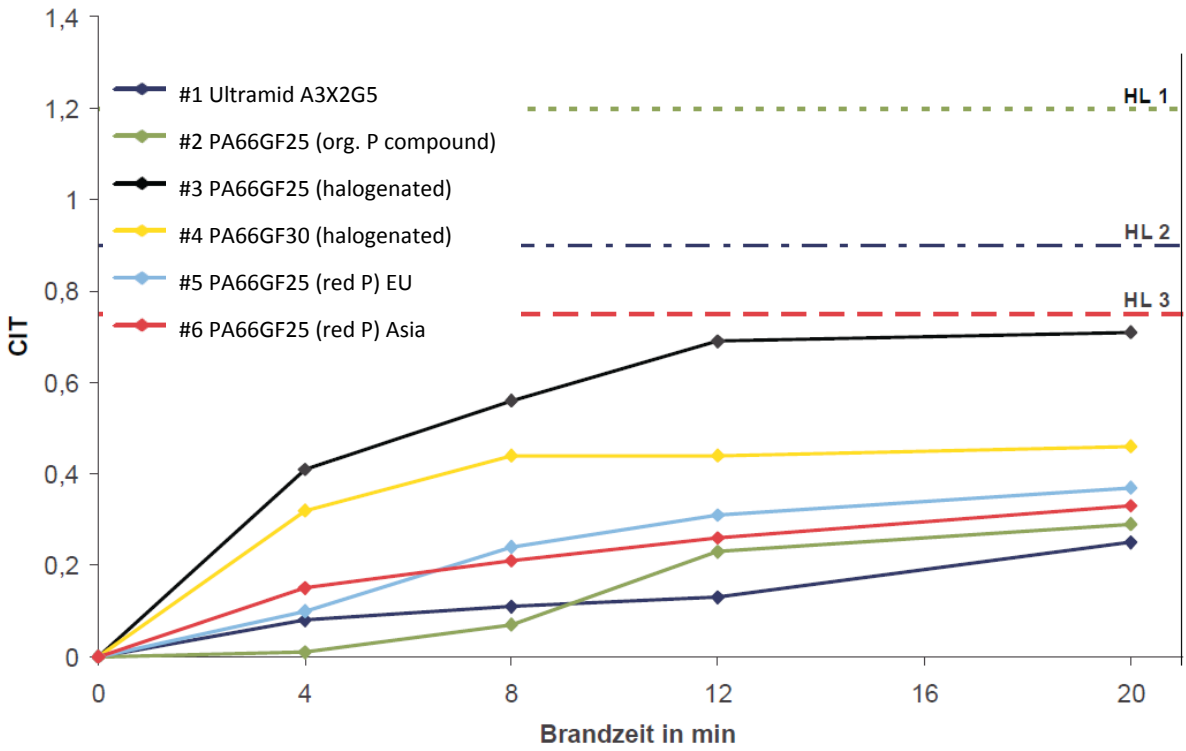
Ultramid® A3X2G5 extincted most rapidly and had the lowest mass loss compared to all other materials. The smoke density was slightly higher than for Compound #2 (org. P compound), the value of CIT, however, was lower at the end the measurement (8-20 min).

The analysis of the flue gases on PH_3 with Draeger tubes yielded in all cases concentrations of < 25 ppm. For Ultramid® A3X2G5 and compound #2 (org. P compound) concentrations of < 1 ppm were detected.

In the semiquantitative determination of PH_3 in the smoke gases of compounds #3 and #4 (halog. FR), and #5 and #6 (red P) the measuring range of Draeger tubes of 0.01-1ppm has been exceeded. In a new trial, using Draeger tubes with a measuring range from 25-900 ppm, no PH_3 was detected. Therefore, the concentration was between 1 and 25 ppm.

However, as compounds #3 and #4 do no contain phosphorus, a cross sensitivity of PH3 Draeger tubes must be assumed.

Fig 7.8 CIT Values for FR / polymer systems



Judging the CIT results in relation to the most sensitive threshold value (HL3, table 7-2) of CEN/TS 45545-2, all examined materials are below the CIT value of 0.75. For the determination the CIT value after 4 or 8 min are considered, but even the CIT values after 20 min are still below this limit for all compounds.