Draft Risk Profile for Dechlorane Plus and its isomers

presentation by the chairs and drafters of the intersessional working group

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POPRC-16 Pre-meeting 1-3 December 2020

STOCKHOLM CONVENTION

Background

- Proposal by Norway in May 2019 to list Dechlorane Plus (CAS No: 13560-89-9) and its *syn*- (CAS No:135821-03-3) and *anti*-isomers (CAS No:135821-74-8) in the Convention

- Proposal evaluated against Annex D criteria at POPRC-15 (Decision POPRC-15/2);
  - Annex D screening criteria fulfilled
  - Intersessional working group established to prepare a draft risk profile (Annex E)
  - Issues related to the inclusion of Dechlorane Plus and its isomers should be dealt with in developing the draft risk profile

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Preparation of draft Risk Profile

- Developed using:
  - Annex D nomination report + input by POPRC-15
  - Annex E submissions
  - Comments from Working Group and Parties
  - Open literature search - peer-reviewed scientific publications and grey literature including e.g. reports and assessments

- Three rounds with comments received (see POPRC.16/INF/4), and four drafts prepared between mid January and early June 2020

- Relevant documents: POPRC.16/2, POPRC.16/INF/4

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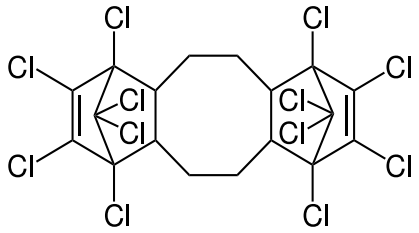
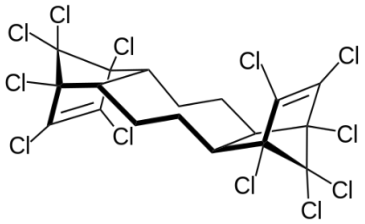
Chemical identity and structure

- Intentionally produced chlorinated flame retardant (no natural sources)
- Commercial Dechlorane Plus™ is a mixture of *syn*- and *anti*-DP
- General chemical formula: $C_{18}H_{12}C_{12}$

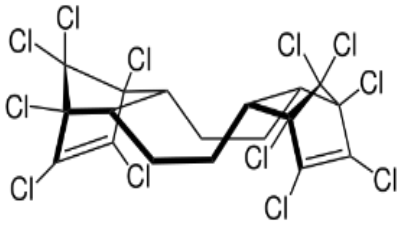
Dechlorane Plus (Cas no. 13560-89-9)



Anti- (or *exo*) Dechlorane Plus (Cas no. 135821-74-8)



Syn- (or *endo*) Dechlorane Plus (Cas no. 135821-03-3)



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Production and use

- Additive flame retardant produced since 1960s
- Originally two known manufacturers globally, today only one
- High volume chemical with global production ~5000 tonnes per year.
- Used in:
  - Electrical cables and coatings
  - Plastic roofing materials
  - Connectors in TV and computer monitors
  - Plastic polymers
  - Automobiles and aviation

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Selected physical-chemical properties

Low water solubility and very hydrophobic - binds to particles/sediment

Property	Value	Reference
Physical state at 20 °C and at 101.3 kPa	Solid white powder	ECHA, 2017d
Melting point	340-382 °C, 350 °C	ECHA, 2017d, OxyChem, 2004b
Vapour pressure	0.006 mm Hg ≙ 0.8 Pa at 200 °C	ECHA, 2017d, OxyChem, 2004b
Water solubility	<1.67 ng/L (20 – 25 °C) 0.044 – 249 µg/L (insoluble)	ECHA, 2017d OxyChem, 2004b
n-Octanol/water partition coefficient (logK_{ow})	9.3	OxyChem, 2004b
Octanol-air partition coefficient K_{oa} (log value)	12.26	OxyChem, 2004b
Sediment/water partition coefficient, (log K_p)	6.65	OxyChem, 2004b
Air/water partition coefficient, (log K_{aw})	Log K_{aw} values estimated at 25 °C: -3.2, 0.44, -2.8 and -3.5	ECHA 2017d

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Releases to the environment

- Emissions occur from a wide variety of sources during all life cycle stages - estimates vary
  - Production
  - Industrial and professional use
  - Service life of consumer products
  - Waste (articles upon becoming waste, waste water treatment, leachate from landfills)

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Global emission scenarios by Hansen et al. 2020

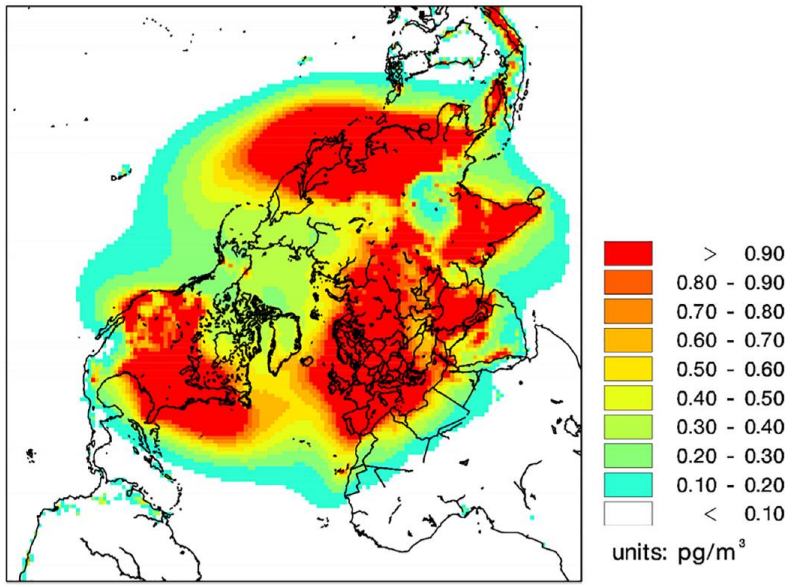

Fig. 2. Predicted annual average atmospheric surface concentrations of DP for 2013 with the high emission scenario.

Hansen et al. 2020. Sci Total Environ. 10;742:140677 (New!)

- One high and one low emission scenario based on production, usage and disposal data
- Geographical distribution also predicted
- Total DP emission predicted to:
  - Low scenario - 0.02 t/year
  - High scenario - 3.2 t/year
- Predicted concentrations evaluated against measurements from the Arctic
- High emission scenario compared best with measurements

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Persistence

- DP is relatively photo-stable in natural light and hydrolysis is not a relevant degradation process

- Persistent in water, soil, sediment (and air):
  - Estimated photolytic half-life in water >24 years (Oxychem, 2007; Sverko et al., 2011)
  - Estimated half-lives in water, soil and sediment predicted to 180, 3650 and 1621 days, respectively (Zhang et al., 2016).
  - Degradation in aging soil of 4.2-8.2% after 260 days with modelled half-life of 1325-2948 days (Cheng et al., 2019)
  - Half-life in suspended sediment ~17 years (Sverko et al., 2008)
  - Present in sediment cores >30 years after initial deposition (Qiu et al, 2007)

- Identified as being persistent in assessments by the EU and Canada (ECHA, 2017; Canada, 2019)

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Bioaccumulation

- Bioaccumulation metrics:
  - BCF > 5000 (Wang et. al 2019)
  - BAF (bioaccumulation factors) >5000
  - Log BAF ≈ 9 (log BAF > 3.7 indicate bioaccumulation)
  - Log Kow for DP is 9.3 (log Kow > 5 indicate bioaccumulation)

- Studies on amphipods in the Norwegian Arctic (Carlsson et al., 2018) showed high log BAFs (amphipod-water) of 8.9 and 9.1 for *syn*- and *anti*-DP, respectively

- Several field studies show BMF or TMF >1, indicating bioaccumulation

- Identified as being bioaccumulative in assessments by the EU and Canada (ECHA, 2017; Canada, 2019)

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Biomagnification (BMFs and TMFs)

Specie or food web	Tissue	BMF	TMF	Reference
Fish/zoo plankton	whole	0.1 – 11		Tomy et al., 2007
Fish/diporeia (shrimp-like)	whole	0.1 - 12		Tomy et al., 2007
Fish/zoo plankton	whole		> 1	Kurt-Karakus et al., 2019
Fish/invertebrate	various		6.5 – 11.3	Wu et al., 2010
Fish/invertebrate (seven species)	whole		1.9 – 3.1	Wang et al., 2015
Fish (various)/crab	various	1.3 – 11.8	2.31*	Sun et al., 2015
Food web (fish, octopus, crab)	muscle	2.3 – 7.1		Sun et al., 2017
Fish diet study	serum	1.0 – 1.2		Tang et al., 2018
Seal/algae (total nine species) Antarctic	various		2.9 – 3.3	Na et al., 2017
Ectotherms /(lizards or snake/insects) remote Mongolia	Muscle/whole	55.9 - 88		Chen et al., 2020
Frog/insects	muscle/whole	1.8 – 2.7		Wu et al., 2018

*Not significant, p= 0.07

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Long Range Transport

- No empirical data for half-life in air available

- Modelled predictions of half-life in air does not adequately consider particle binding:
  - 14 hours based on gas phase reactions and not considering particle-bound DP (Sverko et al., 2011).
  - <0.5 day for photolysis and 160 days for ozone reaction (Canada, 2019)
  - sorption to particles prolong the half-life of DP in air (Sverko et al. 2011)

- The OECD POPs Screening Tool estimates 98.82% partitioning of DP to aerosols and that DP has transport and persistence properties in the range of listed POPs

- Other substances with similarly low vapour pressure (e.g. decaBDE) show significant long-range transport potential (Brevik et al. 2006; POPRC.10/10/Add.2; POPRC-10/2)

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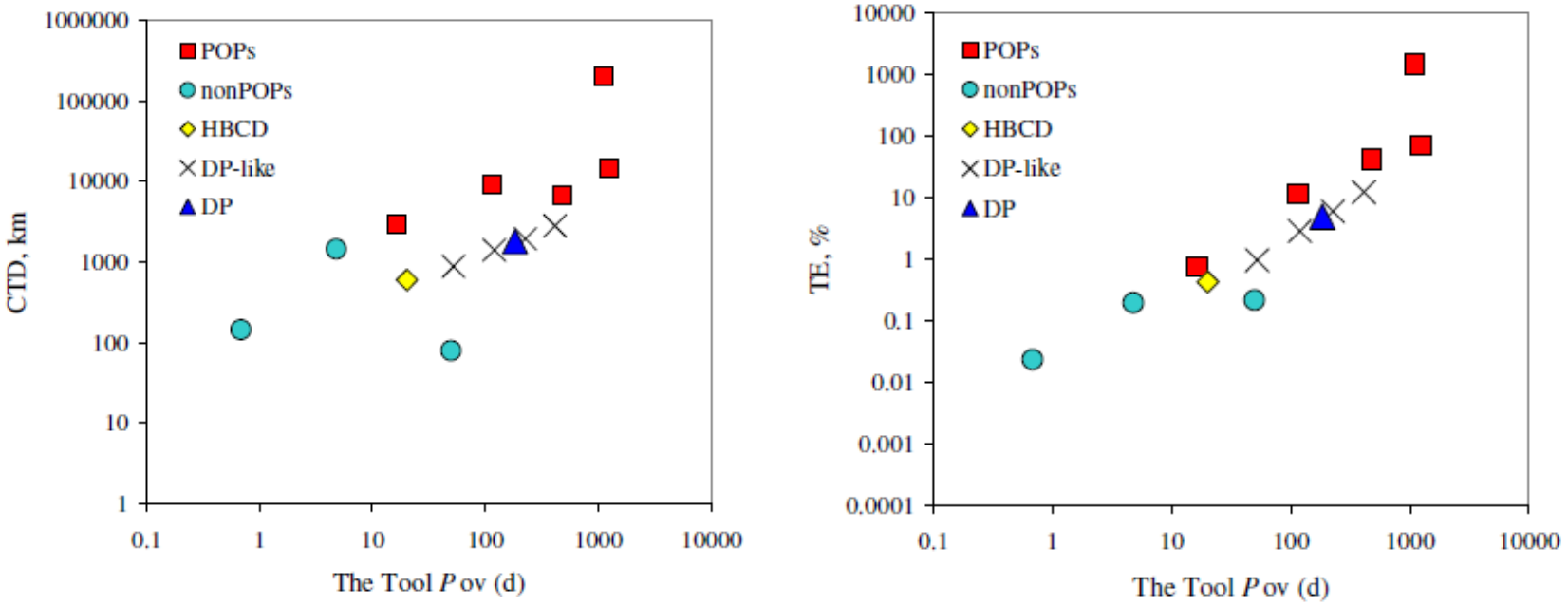
Results for DP obtained with the OECD POPs Screening Tool assuming 100 % emission to air

Figure SI-2: Characteristic travel distance (CTD; km), transfer efficiency (TE, %), and overall persistence (POV; d) of DP, DP analogs, and benchmark chemicals calculated with The OECD Tool assuming that 100% of the chemical emissions are to air.



Sverko et al., 2011, Env. Sci Technol. 2011, 45,5088-98

Long Range Transport

- DP is detected in the environment and biota in remote areas; in the Arctic, Antarctic and a remote mountain area in Tibet (see also POPRC.16/INF/14);

- High degree of particle binding reported - 79 to 99 % in air (Hoh et al. 2006; Ren et al., 2008; Möller et al., 2010) and 80 to 97 % in seawater (Möller et al., 2010).

- Occurrence of DP in remote areas and ocean air ascribed to DP undergoing LRAT (e.g. Möller et al, 2010; Möller et al, 2011; Salamova et al., 2014; Xiao et al., 2012; AMAP, 2017; Canada, 2019)

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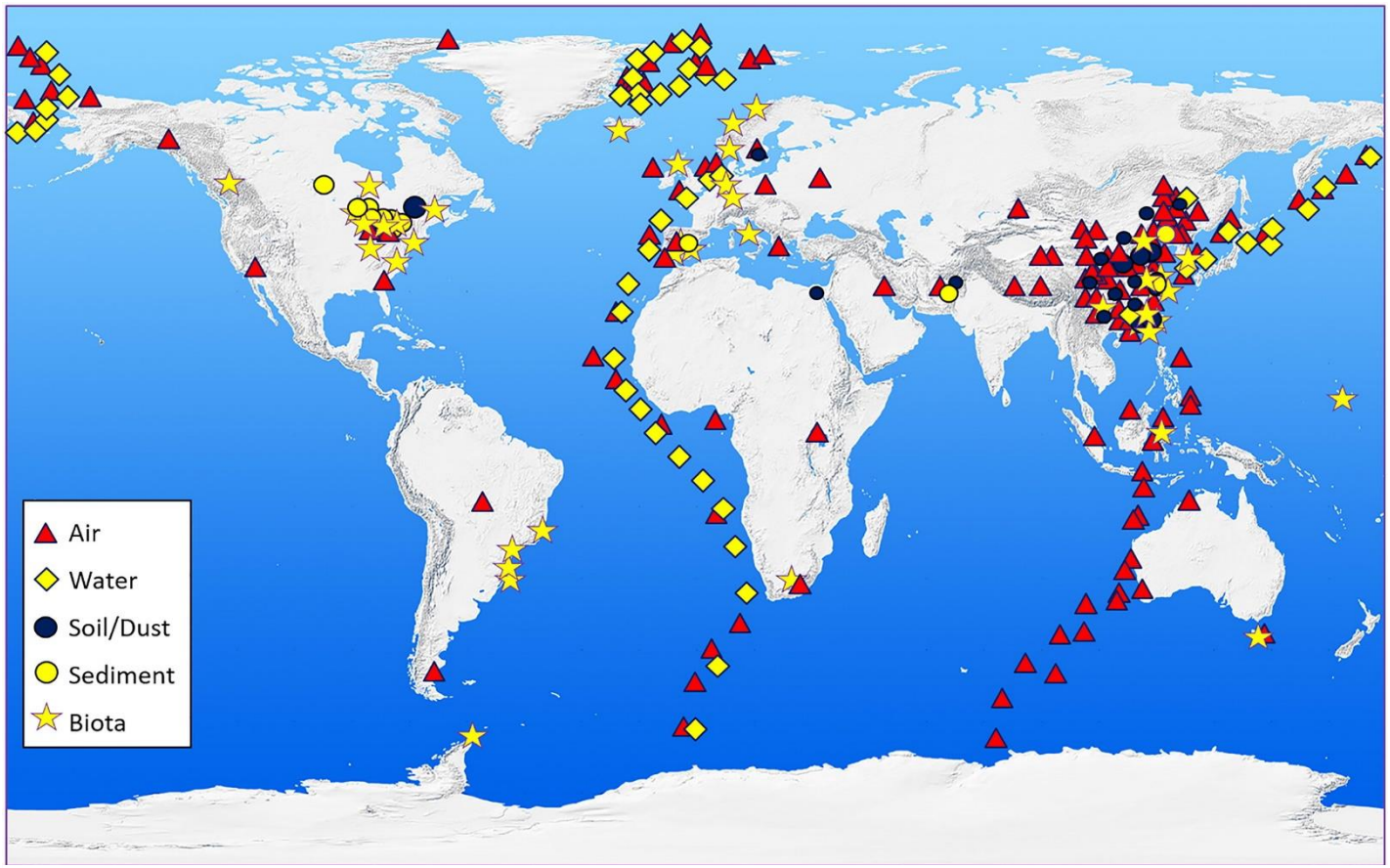
Environmental levels and trends

DP is a global contaminant



Global distribution of DP sampling sites as shown in Wang et al. Env. Intern. 2016, Vol. 88, pp. 206-220

STOCKHOLM CONVENTION

Environmental levels and trends

- DP is detected worldwide in biota and environmental samples (see also POPRC.16/INF/14);
  - Production sites, recycling facilities, in industrial areas, urban, rural and remote areas
  - Air, water, sediment and sewage sludge, soil and dust
  - Terrestrial and aquatic biota – plants, birds, mammals, fish etc
- Data are available from several global regions, but mostly North-America, Europe, Asia, the Arctic, Antarctic and global oceans
- Highest levels and exposure in urban areas, urban industrial areas and near recycling sites and production plants
- Levels in remote regions are typically low, and atmospheric DP levels in the Arctic is comparable to PBDEs (AMAP, 2017)

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Environmental levels and trends

- DP first detected in the environment in 2006 -> limited data for temporal trend analysis

- Temporal trends in the environment and biota are not consistent:
  - several studies show increasing trends, but also decreasing, stable or no trends reported
  - differences in study design -> studies reflect different emission sources, food choices, locations and species are not the same
  - confounded by concentrations near detection levels

- Stable levels found in human serum over time - no significant trend

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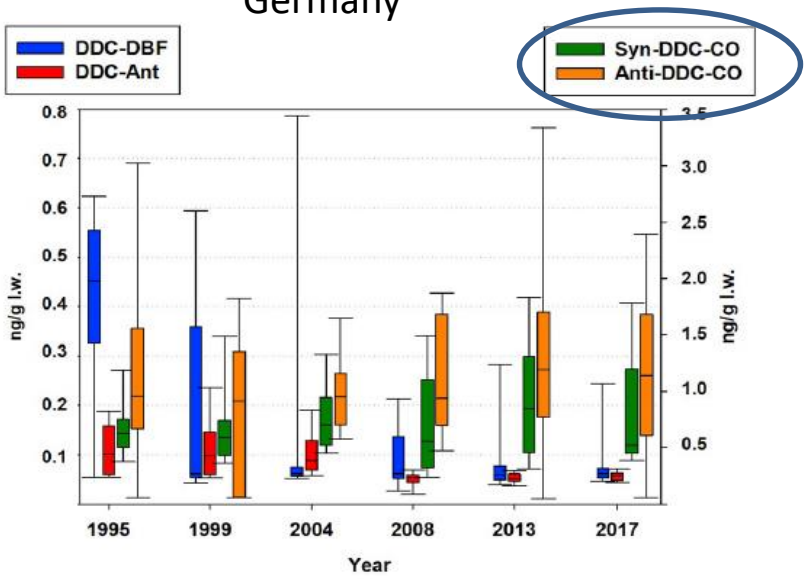
Trend data human serum

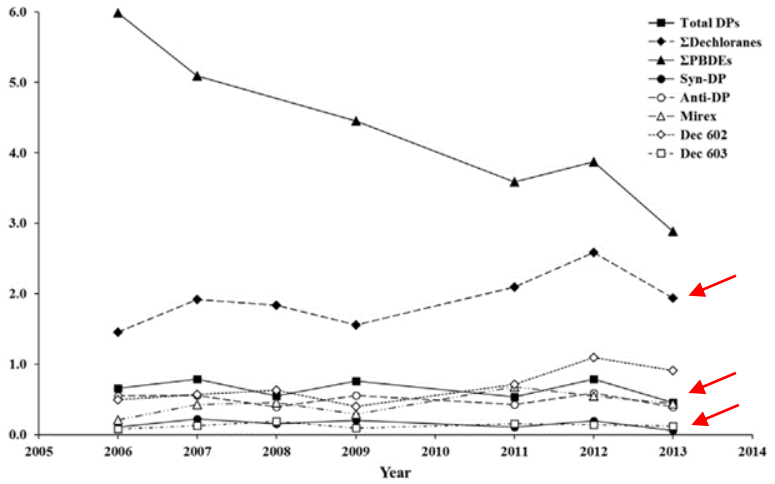
Two trend studies identified, no significant trend for DP observed

Germany



Fromme et al., 2020 (new)

South-Korea



Kim et al., 2016

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Human exposure

- Humans may be exposed to DP from indoor dust, food, indoor and ambient air, water, soil, sediment and breast milk
- Found in human serum/plasma, placenta, cord blood, breast milk
- High exposures in toddlers and young children
- Also high occupational exposures (e.g. manufacturing plant, e-waste recycling sites)

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Adverse effects - Short overview

- Oxidative damage observed across species (algae, bivalves, fish, earthworms, birds, mice, rats)
- Potential for endocrine disruption (fish, mice, humans)
- Neurotoxicity indicated in zebrafish and earthworms
- Liver and adipose tissue impairments (mice and rats)
- Crosses the blood-brain barrier in fish and frogs
- Maternal transfer with exposure of embryo/developing organism at vulnerable stages (fish, frog, birds, shark, human)
- Increased toxicity and bioaccumulation indicated for DP in one mixture toxicity study with PAH - suggest additional cause for concern

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Hazard Assessment - Aquatic ecotoxicity

- Empiric aquatic toxicity tests performed at concentrations above water solubility → some uncertainty, but also some oral studies available.

  - Oxidative stress observed in fish, marine bivalves, algae
  - Indications of neurotoxicity in zebrafish and carp
  - Damage to motor neuron and muscle observed in developing zebrafish larvae
  - Liver impairments observed in fish
  - Potential for endocrine modulating effects in zebrafish
  - Indication of immune modulating effects in carp
  - Effects on photosynthetic activity in marine macroalgae

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Adverse effects – Mammals and humans

- Available studies indicate low concern for reprotoxic effects or acute toxicity via the oral, inhalation and dermal routes of exposure, however studies exceeding 90 days of exposure is still missing.

- *In vivo* repeated high dose exposure of mice and rats indicates effects on liver and liver metabolism and serum parameters (ALP, ALT, total bile acid and glucose)

- Effects on adipocytes and gut microbiota metabolism has been observed after repeated low dose exposure of mice and rats - further evidence for possible obesogenic effects (Peshdary et al., 2020)

- Epidemiology studies indicate possible association between serum DP levels and thyroid or sex hormone homeostasis- further evidence in (Guo et al., 2018; 2020)

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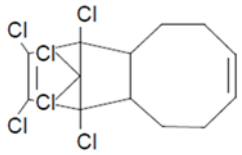
Other concerns - Impurities



- Impurities are formed during production of DP by Diels-Alder reaction
- The impurity DP-monoadduct (DPMA) has been observed in concentrations approximately 2 orders of magnitude higher than DP in the environment e.g:
  - In trout sampled in Lake Ontario, Canada (Sverko et al., 2010).
  - In peregrine falcon eggs from Spain and Canada with concentrations from 1.7 to 469 ng/g lw and 1.2 to 1660 ng/g lw, respectively (Guerra et al., 2011).
- DPMA is potentially bioaccumulative and persistent and structural similarity to aldrin and heptachlor indicates potential for neurotoxicity and/or hepatotoxicity

Conclusions

- DP is a global contaminant that is detected in a variety of biota and environmental samples
- It has many applications and emissions occur during production, use and disposal and management of waste
- It is persistent, bioaccumulate and undergo long-range environmental transport to remote regions
- Adverse effects relates to observed effects on the liver and endocrine system, in particular to the thyroid hormone system and peroxisome proliferator-activated receptor gamma pathway. In aquatic organisms, effects on the developing nervous system and brain have been indicated

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Concluding Statement

Dechlorane Plus with its *syn*- and *anti*-isomers, as a result of their long-range transport, are likely to lead to adverse human health and environmental effects such that global action is warranted.

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Environmental levels - S1

Media	Years (not continuous)	Concentration range
Air (pg/m3)	2004-2011	<DL – 26 734
Water (pg/L)	1974-2010	<DL – 1 740
Sediment (ng/g dw)	~1975-2011	Syn-DP: <DL – 720, Anti-DP: <DL –2640
Soil (ng/g dw)	2006-2010	<DL – 13 400
Biosolids (ng/g dw)	2002-2010	0.31 – <200
Wastewater, effluent, storm water (ng/L)	2009-2010	<DL – 1.2
Biota – aquatic (ng/g lw)	1979-2011	<DL – 1971
Biota – terrestrial and avian (ng/g lw)	2000-2010	<DL – 3820

Source: Canada, 2019

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Adverse effects – Mammals - S2

- Available studies indicate low concern for acute toxicity via the oral, inhalation and dermal routes of exposure, however studies exceeding 90 days of exposure is still missing.

- *In vivo* repeated dose exposure of mice and rats indicates effects on liver and liver metabolism
- In mice (Wu et al., 2012); 10 days oral exposure
  - increase in relative liver weight
  - Liver impairments such as oxidative stress and damage
  - Alteration of gene expression related to carbohydrate, lipid, nucleotide and energy metabolism and signal transduction processes

- In rats, Li et al., (2013b); 90 days oral study
  - altered serum parameters (ALP, ALT, total bile acid and glucose)
  - gene expression of biotransformation enzymes were reduced

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Adverse effects – Mammals - S3

Low doses of DP show potential obesogenic effects observed *in vivo*

- In mice DP (10, 100 or 1000 μg/kg) for 28 days altered glucose metabolism and lipid tissue in a way indicative for development of type 2 diabetes. (Peshdary et al., 2020)
  - promoted glucose intolerance in mice fed high-fat diet independent of weight gain
  - induced development of hypertrophied white adipose tissue
  - DP induced "whitening" of brown adipose tissue
- In rat fed 5 mg/kg /d through pregnancy and/or lactation- in all DP exposure groups, the gut microbiota production of metabolites of short-chain fatty acids was dramatically increased. DP exposure not only altered the gut microbiota structures, but also immensely influenced metabolic functions, causing long-term impact to offspring (Zhang et al., 2020.)

- *In vitro,* DP (at 10 μM) directly activate peroxisome proliferator-activated receptor-γ (PPAR-γ) and induced adipogenesis in isolated pre-adipocytes from mouse and human (Peshdary et al., 2018). DP directly inhibited insulin signalling in murine adipocytes and human primary subcutaneous adipocytes at environmental relevant doses (100 and 1000 nM) (Peshdary et al., 2020).

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Adverse effects – Epidemiology - S4

Epidemiology studies indicate possible association between serum DP levels and thyroid or sex hormone homeostasis

- Association between total triiodothyronine and DP (Ben et al., 2014)
- Association between serum DP levels and expression of iodothyronine deiodeinase I in children (Guo et al., 2020), and adults (Guo et al., 2019).
- lower levels of TSH, thyroid binding globulin and mRNA expression of thyroid receptor (TRα) (Guo et al., 2019)
- Association between *anti*-(DP) levels in wristbands and serum thyroid-stimulating hormone (TSH) in female adults from North- America (Wang et al., 2019)

One study indicate significant association between serum DP levels and sex hormones (Guo et al., 2018).

- Follicle stimulating hormone (FSH) reduced in both male and female
- Estrogen showed a significant non-monotonic in females
- Testosterone was increased in males in association with *anti*-DP levels and showed a nonmonotonic relationship to *syn*- DP serum levels

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Half-life in biota (days) - S5

Species	tissue	Syn-DP	Anti-DP	references
Rainbow trout	whole body minus liver	50-70	30-40	Tomy et al., 2008
Carp	muscle	6.3	7.2	Wang et al., 2019
Marine green macroalgae		1.46	14.53	Gong et al., 2018
Marine green macroalgae		2.1	2.9	Zhao 2014
Rat	liver	179	-*	Li et al., 2013b
Rat	muscle	44	54	Li et al., 2013b
Rat	serum	24	25	Li et al., 2013b

* Depuration time for *anti*-DP for the liver was not calculated due to a non-significant increase in liver after depuration

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