Hazardous Waste and Toxics Reduction Program Technical Memo

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TO:	Joe Fitzgibbon, Chair, House Environment & Energy Committee Reuven Carlyle, Chair, Senate Environment, Energy & Technology Committee
FROM:	Washington State Department of Ecology Craig Manahan, Hazardous Waste and Toxics Reduction Program
CC:	House Environment & Energy Committee members Senate Environment, Energy & Technology Committee members
SUBJECT:	Technical Memo: Assessment of potential hazards of 6PPD and alternatives

Background

Urban runoff mortality syndrome (URMS), also known as Coho pre-spawn mortality, is a condition where Coho salmon die prior to spawning. Observers have described the condition in urban streams since the late 1980s (Dunagan, 2020). URMS is directly related to urbanization density, specifically proximity to roadways. Roadway runoff contains a mixture of chemicals that pollutes streams during rain events and is shown to cause URMS. The lethal effects of roadway runoff affect both pre-spawn and juvenile salmon, and are harmful to many other species of aquatic organisms.

While scientists narrowed the source of URMS to roadway runoff, UW and WSU scientists only recently identified the specific chemical apparently responsible in a paper published in January 2021 (Tian et al, 2021). The chemical, 6PPD-quinone, is a transformation product of 6PPD, which is used as an anti-degradant in almost every automobile tire on the road. 6PPD-quinone is toxic to Coho salmon at very low concentrations (less than 1 part per billion). Concentrations of 6PPD-quinone in urban streams in cities such as Seattle, San Francisco, and Los Angeles frequently exceed this level, particularly during storm events.

In 2021, the Washington State Legislature passed an operating budget proviso allocating $195,000 to Ecology to assess "potential hazards of 6PPD and other chemical classes and breakdown products used as antioxidants and/or antiozonants in tires."[1] This technical memo fulfills that assignment.

[1] See Section 302 (22) of https://lawfilesext.leg.wa.gov/biennium/2021-22/Pdf/Bills/Session%20Laws/Senate/5092-S.SL.pdf.

Methods

We identified alternative chemicals with potential for use in tire manufacturing from peer reviewed journal articles, government reports, and conversations with manufacturers and manufacturer associations. We did not prioritize potential alternatives or consider preliminary technical performance details. We selected alternatives if the source recommended them as having promise as an anti-degradant compared to 6PPD, or if they were known to be used as an anti-degradant in tires currently or in the past.

We provided the list of potential alternatives to stakeholders—including manufacturers, non-governmental organizations, and other governmental agencies—for additions and comments prior to writing the report in order to incorporate their perspective. We listed the chemicals selected and rationale in Table 1.

Table 1: Summary of chemicals assessed and rationale for selection.

Chemical	CASRN	Rationale for selection
6PPD [N-(1,3-Dimethylbutyl)-N'-phenyl-p-phenylenediamine]	793-24-8	Chemical of concern
6QDI [N~1~-(4-Methylpentan-2-yl)-N~4~-phenylcyclohexa-2,5-diene-1,4-diimine]	52870-46-9	California Department of Toxic Substances Control (DTSC) 6PPD Product-Chemical Profile 2021
IPPD [N-Isopropyl-N'-phenyl-p-phenylenediamine]	101-72-4	DTSC 2021, Zhang et al. 2021, Huang et al. 2021
77PD [N,N'-Bis(1,4-dimethylpentyl)-4-phenylenediamine]	3081-14-9	Communication from US Tire Manufacturer's Association 2021, Zhang et al. 2021, Huang et al. 2021
CCPD [N,N'-Dicyclohexyl-4-phenylenediamine]	4175-38-6	Communication from US Tire Manufacturer's Association 2021
7PPD [N-(5-Methyl-2-hexyl)-N'-phenyl-p-phenylenediamine]	3081-01-4	DTSC 2021
TMQ [1,2-Dihydro-2,2,4-trimethylquinoline]	147-47-7	DTSC 2021
NBC [Nickel dibutyldithiocarbamate]	13927-77-0	DTSC 2021
Ethoxyquin [6-Ethoxy-2,2,4-trimethyl-1,2-dihydroquinoline]	91-53-2	Braden and Gent 1962, Huntink et al. 2004
Dilauryl thiodipropionate	123-28-4	Huntink et al. 2004

We performed chemical hazard assessments to assess the potential hazards of 6PPD and alternatives listed above that could be used as antioxidants and/or antiozonants in tires. Chemical hazard assessments provide an overview of known toxicological hazards of chemicals. GreenScreen® for Safer Chemicals is a method for chemical hazard assessment used to assess and identify chemicals of high concern and safer alternatives. Numerous governmental bodies, industry, and non-governmental organizations use it as part of the alternatives assessment process. A consistent and transparent methodology for chemical hazard assessment allows us to rank chemical hazards in a reproducible way and compare multiple chemicals.

We chose to use GreenScreen® as the method for chemical hazard assessment as it is the industry standard for public and transparent chemical hazard assessments. It also incorporates criteria from authoritative bodies, such as the Globally Harmonized System of Classification and Labeling of Chemicals (GHS) and Environmental Protection Agency (EPA) Safer Choice. A GreenScreen® assessment evaluates the following 19 hazard endpoints (CPA, 2018):

Group I Human

- Carcinogenicity
- Genotoxicity/mutagenicity
- Reproductive toxicity
- Developmental toxicity
- Endocrine activity

Group II Human

- Acute toxicity
- Systemic toxicity (single dose)
- Systemic toxicity (repeat dose)
- Neurotoxicity (single dose)
- Neurotoxicity (repeat dose)
- Skin sensitization
- Respiratory sensitization
- Skin irritation
- Eye irritation

Ecotoxicity

- Acute aquatic toxicity
- Chronic aquatic toxicity

Fate

- Persistence
- Bioaccumulation

Physical

- Reactivity
- Flammability

GreenScreen® assessments use data from peer-reviewed science, authoritative bodies, and regulatory studies (e.g., studies following Organization for Economic Cooperation and Development protocols) to assess toxicity. They may also use toxicity data for chemical analogs/surrogates (which are chemically or biologically suitable substitutes for the chemical under assessment) or modeling data (e.g., the EPA Ecological Structure Activity Relationships Program tool) to fill in data gaps.

For this project, we contracted the hazard assessments with ToxServices, LLC. This allowed for faster results, publicly available assessments, and a thorough review by multiple, third party qualified staff. ToxServices, LLC are certified GreenScreen® assessors that have demonstrated the capacity to provide GreenScreen® assessments on a consulting basis. Ecology has used their services for numerous prior projects, and they have rigorous internal review processes. In addition, Ecology reviewed the assessments and provided comments before finalizing the assessments.

The certified GreenScreen® assessor compiles hazard data and assigns a score for each endpoint based on criteria developed from the GHS and other health and environmental protection agencies (such as EPA). They use the compiled data to assign scores included in the complete GreenScreen® report. Hazard scores are assigned as follows:

- Very low (vL).
- Low (L).
- Moderate (M).
- High (H).
- Very high (vH).
- Data gap (DG), when there is not sufficient data to assign a score.

Furthermore, the assessor gives scores either high confidence (bold font in the summary table), or low confidence (italics in the summary table).

The assessor then uses each hazard endpoint to assign a benchmark (BM) score of 1 to 4 for the chemical. A BM-1 stands for "Avoid: Chemical of High Concern" while a BM-4 means "Prefer: Safer Chemical." They may assign a chemical Benchmark-U (unknown) if there are inadequate data to characterize the chemical under the benchmark criteria, or BM-2_{DG} or BM-3_{DG} if there are inadequate data to meet the data requirements of a higher benchmark score (CPA, 2018). GreenScreen® assessments that result in scores of BM-U, BM-2, BM-3, or BM-4 expire five years after the assessment date and the substance must be re-evaluated (CPA, 2019).

Results

You can access completed GreenScreen® assessments on the EZview site. We summarized results in Table 2.

Table 2: Summary of results of GreenScreen® assessments.

Chemical	CASRN	GreenScreen® Benchmark Score
6PPD	793-24-8	BM-1
6QDI	52870-46-9	BM-1
IPPD	101-72-4	BM-1
77PD	3081-14-9	BM-2
CCPD	4175-38-6	BM-1
7PPD	3081-01-4	BM-1
TMQ	147-47-7	BM-2
NBC	13927-77-0	BM-1
Ethoxyquin	91-53-2	BM-2
Dilauryl thiodipropionate	123-28-4	$BM\text{-}3_{DG}$

6PPD (CAS #793-24-8)

The GreenScreen® hazard assessment ranked 6PPD as a BM-1 chemical, or "Avoid: Chemical of High Concern."

Table 3: GreenScreen® hazard assessment of 6PPD.

Chemical (CASRN)	Carcinogenicity	Genotoxicity/Mutagenicity	Reproductive Toxicity	Developmental Toxicity	Endocrine Activity	Acute Toxicity	Systemic Toxicity (single)	Systemic Toxicity (repeat)	Neurotoxicity (single)	Neurotoxicity (repeat)	Skin Sensitization	Respiratory Sensitization	Skin Irritation	Eye Irritation	Acute Aquatic Toxicity	Chronic Aquatic Toxicity	Persistence	Bioaccumulation	Reactivity	Flammability	Benchmark Score
6PPD 793-24-8	**L**	**L**	**H**	**M**	**M**	**M**	DG	**M**	*M*	DG	**H**	*M*	**L**	**M**	**vH**	**vH**	*H*	**H**	**L**	**L**	**BM-1**

ToxServices scored 6PPD as a BM-1 due to high reproductive toxicity. 6PPD caused dystocia (difficult birth) and/or prolonged labor in rats, leading to deaths in offspring. In addition, 6PPD scored as high for skin sensitization, bioaccumulation, and persistence, though the persistence score was given low confidence because it was based on modeled data. ToxServices identified data gaps in systemic toxicity (single exposure) and neurotoxicity (repeat exposure).

6PPD scored as very high for acute and chronic aquatic toxicity as it had lethal effects on fish with LC_{50}[2] values as low as 0.028 mg/L and subchronic effects at 0.004 mg/L. Tian et al 2021 reported toxicity of 6PPD to Coho salmon with an LC_{50} value of 0.251 mg/L. The EPA database reported an LC_{50} value of 0.14 mg/L for 6PPD towards rainbow trout, another member of the Oncorhynchus genus.[3]

6PPD is the only compound shown to form a quinone transformation product that is much more lethal to Coho salmon. As far as we know, no data has been published on any other chemical used as anti-degradants in tires (including other PPDs) and their ability to form quinone molecules when exposed to ozone. No other details are available about toxicity of 6PPD-quinone itself towards other hazard endpoints besides acute aquatic toxicity.

Tian et al 2021 reported toxicity of 6PPD-quinone towards Coho salmon with an LC_{50} value of just 0.00079 mg/L, or more than two orders or magnitude more toxic to Coho salmon than 6PPD. There is no publicly available information indicating toxicity of 6PPD-quinone towards rainbow trout, or any other members of the Oncorhynchus genus.

6QDI (CAS #52870-46-9)

The GreenScreen® hazard assessment ranked 6QDI as a BM-1 chemical, or "Avoid: Chemical of High Concern."

Table 4: GreenScreen® hazard assessment of 6QDI.

Chemical (CASRN)	Carcinogenicity	Genotoxicity/Mutagenicity	Reproductive Toxicity	Developmental Toxicity	Endocrine Activity	Acute Toxicity	Systemic Toxicity (single)	Systemic Toxicity (repeat)	Neurotoxicity (single)	Neurotoxicity (repeat)	Skin Sensitization	Respiratory Sensitization	Skin Irritation	Eye Irritation	Acute Aquatic Toxicity	Chronic Aquatic Toxicity	Persistence	Bioaccumulation	Reactivity	Flammability	Benchmark Score
6QDI 52870-46-9	**L**	**L**	**H**	**M**	**M**	**M**	*M*	**M**	*M*	DG	**H**	DG	**L**	**H**	**vH**	**vH**	*vH*	**H**	**L**	*L*	**BM-1**

[2] The concentration of a chemical that is expected to kill half of test animals when administered as a single exposure.

[3] https://comptox.epa.gov/dashboard/dsstoxdb/results?search=DTXSID9025114#toxicity-values

ToxServices scored 6QDI as a BM-1 due to very high persistence, very high ecotoxicity (acute and chronic aquatic toxicity), high reproductive toxicity, and high skin sensitization hazard. 6QDI is almost identical in structure to 6PPD as it is the oxidized form of 6PPD. We expect it has similar hazards. The assessment used 6PPD as a surrogate for several endpoints including reproductive toxicity, where 6PPD caused difficult births in rat reproduction.

One differentiation found in the GreenScreen® assessment between 6QDI and 6PPD is in systemic toxicity (single exposure), where a safety data sheet for 6QDI identified it as a respiratory irritant. As a result, ToxServices conservatively assigned 6QDI a moderate hazard for this endpoint with low confidence. Another difference is that 6QDI scored as a high hazard for eye irritation, while 6PPD scored as a moderate hazard. 6QDI is on an authoritative list for this endpoint because it has a "H319—Causes serious eye irritation" classification under the EU's GHS. 6PPD is not on the same list.

ToxServices identified data gaps in neurotoxicity (repeat exposure) and respiratory sensitization.

Modeling showed that 6QDI is likely to be more persistent than 6PPD, so ToxServices gave it a score of very high for this endpoint, though with low confidence. The ability for 6QDI to undergo environmental transformation to form 6PPD-quinone is unknown, but it seems likely to be possible under the right environmental conditions given the similarity in structure between the two chemicals.

IPPD (CAS #101-72-4)

The GreenScreen® hazard assessment ranked IPPD as a BM-1 chemical, or "Avoid: Chemical of High Concern."

Table 5: GreenScreen® hazard assessment of IPPD.

Chemical (CASRN)	Carcinogenicity	Genotoxicity/Mutagenicity	Reproductive Toxicity	Developmental Toxicity	Endocrine Activity	Acute Toxicity	Systemic Toxicity (single)	Systemic Toxicity (repeat)	Neurotoxicity (single)	Neurotoxicity (repeat)	Skin Sensitization	Respiratory Sensitization	Skin Irritation	Eye Irritation	Acute Aquatic Toxicity	Chronic Aquatic Toxicity	Persistence	Bioaccumulation	Reactivity	Flammability	Benchmark Score
IPPD 101-72-4	*L*	**L**	*H*	**M**	*M*	**M**	DG	**M**	*M*	DG	**H**	*M*	**L**	*M*	**vH**	*vH*	*H*	**vL**	*L*	**L**	**BM-1**

ToxServices scored IPPD as a BM-1 due to high reproductive toxicity. However, since insufficient data is available for IPPD itself, the contractor used 6PPD as a surrogate for this endpoint. 6PPD is very similar to IPPD in structure, but it has an additional three carbons, causing it to be slightly larger. ToxServices identified it as a weak surrogate because of this size difference. As mentioned above, 6PPD has caused difficult births in rat reproduction.

ToxServices scored IPPD as high for skin sensitization and persistence, though the persistence score was given low confidence because it was based on modeled data. The contractor also identified data gaps in systemic toxicity (single exposure) and neurotoxicity (repeat exposure).

In addition, ToxServices scored IPPD as very high for acute aquatic toxicity as it had lethal effects on fish as low as 0.34 mg/L. Once again, the contractor used 6PPD as a surrogate for the chronic aquatic toxicity endpoint due to lack of data specific to IPPD, giving it a very high hazard score but low confidence.

It is not currently known if IPPD forms a quinone in the environment with similar acute toxicity to salmon as 6PPD-quinone. IPPD has a 96-hour LC_{50} reported for rainbow trout, another member of the Oncorhynchus genus, at 0.34 mg/L.

77PD (CAS #3081-14-9)

The GreenScreen® hazard assessment ranked 77PD as a BM-2 chemical, or "Use but Search for Safer Substitutes."

Table 6: GreenScreen® hazard assessment of 77PD.

Chemical (CASRN)	Carcinogenicity	Genotoxicity/Mutagenicity	Reproductive Toxicity	Developmental Toxicity	Endocrine Activity	Acute Toxicity	Systemic Toxicity (single)	Systemic Toxicity (repeat)	Neurotoxicity (single)	Neurotoxicity (repeat)	Skin Sensitization	Respiratory Sensitization	Skin Irritation	Eye Irritation	Acute Aquatic Toxicity	Chronic Aquatic Toxicity	Persistence	Bioaccumulation	Reactivity	Flammability	Benchmark Score
77PD 3081-14-9	*L*	**L**	**L**	*M*	DG	**M**	**L**	**M**	*L*	DG	*H*	*M*	**L**	**L**	**vH**	**vH**	*H*	*M*	*L*	**L**	**BM-2**

ToxServices scored 77PD as a BM-2 due to high persistence, moderate bioaccumulation, moderate developmental toxicity, very high acute and chronic aquatic toxicity, and moderate systemic toxicity (repeat exposure). 77PD is a PPD similar to 6PPD, but unlike 6PPD it had limited effects on reproductive toxicity, which was the cause of 6PPD's BM-1 score.

The hazard assessment scored 77PD as moderate for developmental toxicity due to reduced pup body weights and survival in rats at high doses. In addition, 77PD was lethal towards rats with an LD_{50} of 730 mg/kg and caused decreased body weight in rats at 22.82 mg/kg/day over 90 days.

ToxServices identified data gaps in endocrine activity and neurotoxicity (repeat dose).

It is unknown if 77PD forms a quinone similar to 6PPD-quinone in the environment, or if such a compound is acutely toxic to Coho salmon.

ToxServices scored 77PD very high in both acute and chronic toxicity due to a LC_{50} of 0.14 mg/L and a NOEC of 0.018 mg/L in fathead minnows. No data was available for toxicity towards any member of the Oncorhynchus genus.

CCPD (CAS #4175-38-6)

The GreenScreen® hazard assessment ranked CCPD as a BM-1 chemical, or "Avoid: Chemical of High Concern."

Table 7: GreenScreen® hazard assessment of CCPD.

Chemical (CASRN)	Carcinogenicity	Genotoxicity/Mutagenicity	Reproductive Toxicity	Developmental Toxicity	Endocrine Activity	Acute Toxicity	Systemic Toxicity (single)	Systemic Toxicity (repeat)	Neurotoxicity (single)	Neurotoxicity (repeat)	Skin Sensitization	Respiratory Sensitization	Skin Irritation	Eye Irritation	Acute Aquatic Toxicity	Chronic Aquatic Toxicity	Persistence	Bioaccumulation	Reactivity	Flammability	Benchmark Score
CCPD 4175-38-6	*L*	*L*	*L*	*M*	DG	*H*	DG	*H*	*L*	DG	*H*	*M*	*vH*	*H*	*vH*	*vH*	*H*	*H*	*L*	*L*	**BM-1**

ToxServices scored CCPD as a BM-1 due to high persistence, high bioaccumulation, very high acute and chronic aquatic toxicity, very high skin irritation, and high systemic toxicity (repeat exposure).

Very limited data was available for CCPD itself, so the contractor used 77PD and 44PD (CAS #101-96-2) as surrogates for almost all endpoints. They identified data gaps in endocrine activity, systemic toxicity (single dose), and neurotoxicity (repeat dose).

It is unknown if CCPD forms a quinone similar to 6PPD-quinone in the environment, or if such a compound is acutely toxic to Coho salmon.

ToxServices scored CCPD very high in both acute and chronic toxicity due to a LC_{50} of 0.13 mg/L in rainbow trout and a NOEC of 0.096 mg/L in algae for surrogate 44PD. No data was available for CCPD toxicity towards any species.

7PPD (CAS #3081-01-4)

The GreenScreen® hazard assessment ranked 7PPD as a BM-1 chemical, or "Avoid: Chemical of High Concern."

Table 8: GreenScreen® hazard assessment of 7PPD.

Chemical (CASRN)	Carcinogenicity	Genotoxicity/Mutagenicity	Reproductive Toxicity	Developmental Toxicity	Endocrine Activity	Acute Toxicity	Systemic Toxicity (single)	Systemic Toxicity (repeat)	Neurotoxicity (single)	Neurotoxicity (repeat)	Skin Sensitization	Respiratory Sensitization	Skin Irritation	Eye Irritation	Acute Aquatic Toxicity	Chronic Aquatic Toxicity	Persistence	Bioaccumulation	Reactivity	Flammability	Benchmark Score
7PPD 3081-01-4	**L**	**L**	**H**	**M**	**M**	**L**	**L**	**M**	*L*	DG	**H**	*M*	**L**	*M*	**vH**	**vH**	*H*	*L*	*L*	**L**	**BM-1**

ToxServices scored 7PPD as a BM-1 due to high reproductive toxicity. Studies on oral exposure in rats identified total litter loss, longer gestation length, and difficult birth leading to euthanasia in treated females.

The contractor scored 7PPD as high for skin sensitization and persistence, though the persistence score was given low confidence because it was based on modeled data. They identified a data gap in neurotoxicity (repeat exposure).

ToxServices scored 7PPD as very high for acute and chronic aquatic toxicity as it had lethal effects on fish with LC_{50} values as low as 0.3 mg/L and chronic NOECs as low as 0.013 mg/L in algae using a strong surrogate.

It is not currently known if 7PPD forms a quinone in the environment with similar acute toxicity to salmon as 6PPD-quinone. A 96-hour LC_{50} is listed in the GreenScreen® at 0.4 mg/L for rainbow trout, another member of the Oncorhynchus genus. No data is available for Coho salmon toxicity.

TMQ (CAS #147-47-7)

The GreenScreen® hazard assessment ranked TMQ as a BM-2 chemical, or "Use but Search for Safer Substitutes."

Table 9: GreenScreen® hazard assessment of TMQ.

Chemical (CASRN)	Carcinogenicity	Genotoxicity/Mutagenicity	Reproductive Toxicity	Developmental Toxicity	Endocrine Activity	Acute Toxicity	Systemic Toxicity (single)	Systemic Toxicity (repeat)	Neurotoxicity (single)	Neurotoxicity (repeat)	Skin Sensitization	Respiratory Sensitization	Skin Irritation	Eye Irritation	Acute Aquatic Toxicity	Chronic Aquatic Toxicity	Persistence	Bioaccumulation	Reactivity	Flammability	Benchmark Score
TMQ 147-47-7	**M**	**L**	*M*	*M*	DG	**M**	**vH**	**H**	DG	DG	*L*	*L*	*L*	*L*	*H*	*H*	*H*	**vL**	*L*	**L**	**BM-2**

ToxServices scored TMQ as a BM-2 due to high persistence, moderate group I toxicity (carcinogenicity, reproductive, and developmental), and very high systemic toxicity (repeat dose).

The contractor gave high persistence a low confidence score due to limited experimental data and use of modeling. TMQ caused effects on the liver, kidney, and bladder in repeated dose experiments, leading to a very high systemic toxicity score. A two-year carcinogenicity study conducted on rats found higher incidences of renal carcinoma in treated animals, leading to a moderate hazard score for the carcinogenicity endpoint. ToxServices identified data gaps in endocrine activity and neurotoxicity (single and repeat dose).

The assessment scored TMQ as high for acute and chronic aquatic toxicity, though the scores were given low confidence due to the use of weak surrogates and modeling.

TMQ is not a PPD type molecule, so it should not be able to form a quinone similar to 6PPD-quinone in the environment. No data is available for Coho salmon toxicity, or toxicity towards other members of the Oncorhynchus genus.

NBC—Nickel Dibutyldithiocarbamate (CAS #13927-77-0)

The GreenScreen® hazard assessment ranked NBC as a BM-1 chemical, or "Avoid: Chemical of High Concern."

Table 10: GreenScreen® hazard assessment of NBC.

Chemical (CASRN)	Carcinogenicity	Genotoxicity/Mutagenicity	Reproductive Toxicity	Developmental Toxicity	Endocrine Activity	Acute Toxicity	Systemic Toxicity (single)	Systemic Toxicity (repeat)	Neurotoxicity (single)	Neurotoxicity (repeat)	Skin Sensitization	Respiratory Sensitization	Skin Irritation	Eye Irritation	Acute Aquatic Toxicity	Chronic Aquatic Toxicity	Persistence	Bioaccumulation	Reactivity	Flammability	Benchmark Score
NBC 13927-77-0	*H*	**L**	*M*	*L*	DG	**L**	**L**	**H**	*M*	*L*	**L**	*M*	**L**	*H*	**L**	*L*	*vH*	*L*	*L*	**L**	**BM-1**

ToxServices scored NBC as a BM-1 due to very high persistence, high carcinogenicity, and high systemic toxicity (repeat dose).

The contractor scored NBC as high for carcinogenicity due to multiple authoritative listings of nickel compounds as a group being carcinogenic. However, due to an 18-month study on mice returning negative results for carcinogenicity, this endpoint score was given low confidence. ToxServices did not find the 18-month study sufficient to overrule an authoritative listing, since two-year studies are standard in carcinogenicity investigations.

The assessment scored NBC as high for systemic toxicity (repeat dose), due to effects on heart and skeletal muscle occurring at 2 mg/kg/day. Due to the presence of an inorganic metal, we expect NBC is recalcitrant in the environment. A test in activated sludge supports this, but the score of very high persistence was given low confidence to a lack of experimental data.

ToxServices identified a data gap in endocrine activity.

Acute and chronic aquatic toxicity were low in identified data and NBC was assigned a low hazard score for these endpoints. NBC is not able to form a quinone form in the environment, since it is not a PPD, but specific toxicity towards Coho salmon is unknown. Toxicity towards rainbow trout, another member of the Oncorhynchus genus, was greater than 100 mg/L in the ECOTOX database.[4]

[4] https://comptox.epa.gov/dashboard/dsstoxdb/results?search=DTXSID2020927#toxicity-values

Ethoxyquin (CAS #91-53-2)

The GreenScreen® hazard assessment ranked ethoxyquin as a BM-2 chemical, or "Use but Search for Safer Substitutes."

Table 11: GreenScreen® hazard assessment of ethoxyquin.

Chemical (CASRN)	Carcinogenicity	Genotoxicity/Mutagenicity	Reproductive Toxicity	Developmental Toxicity	Endocrine Activity	Acute Toxicity	Systemic Toxicity (single)	Systemic Toxicity (repeat)	Neurotoxicity (single)	Neurotoxicity (repeat)	Skin Sensitization	Respiratory Sensitization	Skin Irritation	Eye Irritation	Acute Aquatic Toxicity	Chronic Aquatic Toxicity	Persistence	Bioaccumulation	Reactivity	Flammability	Benchmark Score
Ethoxyquin 91-53-2	*L*	**L**	*M*	*M*	**M**	**M**	**vH**	**H**	DG	DG	**M**	DG	**L**	**L**	**H**	*H*	*H*	**vL**	**L**	**L**	**BM-2**

ToxServices scored ethoxyquin as a BM-2 due to high persistence, moderate group I toxicity (reproductive, developmental, and endocrine activity), and very high systemic toxicity (single dose).

Ethoxyquin had effects on number of litters, gestation length, and pup body weight in rats, though these were at higher doses that also caused maternal toxicity. Ethoxyquin has been shown to have some effect on androgenic activity in vitro, though it is unclear if this leads to any potential health effects. Ethoxyquin was lethal to rats with an LD_{50} of 800 mg/kg. Dogs that received a single dose of 100 mg/kg or 2 mg/kg/day saw an alteration of blood chemistry, leading to liver damage.

ToxServices identified data gaps in neurotoxicity (single and repeat exposure) as well as respiratory sensitization. Ethoxyquin was scored as high hazard for persistence, but this was based on modeled data, so a low confidence score was assigned.

Ethoxyquin has not been shown to be as toxic to aquatic organisms as 6PPD, with the most conservative value identified at 2 mg/L in water fleas, although it still scores as a high hazard for both acute and aquatic toxicity. Ethoxyquin is not a PPD like many of the other compounds assessed, so it is unlikely to form a transformation product similar to 6PPD-quinone that is much more toxic to Coho salmon.

There is no data for ethoxyquin toxicity towards Coho salmon, but it has a listed LC_{50} of 18 mg/L towards rainbow trout, another member of the Oncorhynchus genus.

Dilauryl Thiodipropionate (CAS #123-28-4)

The GreenScreen® hazard assessment ranked Dilauryl Thiodipropionate as a BM-3 chemical, or "Use but Still Opportunity for Improvement."

Table 12: GreenScreen® hazard assessment of Dilauryl Thiodipropionate.

Chemical (CASRN)	Carcinogenicity	Genotoxicity/Mutagenicity	Reproductive Toxicity	Developmental Toxicity	Endocrine Activity	Acute Toxicity	Systemic Toxicity (single)	Systemic Toxicity (repeat)	Neurotoxicity (single)	Neurotoxicity (repeat)	Skin Sensitization	Respiratory Sensitization	Skin Irritation	Eye Irritation	Acute Aquatic Toxicity	Chronic Aquatic Toxicity	Persistence	Bioaccumulation	Reactivity	Flammability	Benchmark Score
Dilauryl Thiodipropionate 123-28-4	*L*	**L**	*L*	**L**	DG	**L**	**L**	**L**	*L*	DG	**L**	*L*	**L**	**L**	**L**	*L*	**L**	*vL*	*L*	**L**	**BM-3$_{DG}$**

ToxServices scored dilauryl thiodipropionate as a BM-3$_{DG}$ due to low or very low scores in all endpoints, but with data gaps in endocrine activity and neurotoxicity (repeat dose). These data gaps prevent assigning a score of BM-4, resulting in the BM-3$_{DG}$ ranking. In order to achieve a score of BM-4, data is required in all endpoints.

The hazard assessment scored dilauryl thiodipropionate as low hazard for acute and chronic aquatic toxicity due to low toxicity in all three trophic levels (fish, invertebrate, and algae), although modeling was used for chronic exposure, leading to a low confidence level for that endpoint.

Dilauryl thiodipropionate is not a PPD type molecule, so it should not be able to form a quinone similar to 6PPD-quinone in the environment. No data is available for Coho salmon toxicity, or toxicity towards other members of the Oncorhynchus genus.

Discussion

A major data gap with all of the listed alternatives is that they have not been tested as a cause of urban runoff mortality syndrome in Coho salmon, which is the main reason for replacing 6PPD. The potential to contribute to URMS seems particularly likely with other PPD compounds due to their similar structure to 6PPD, but transformation products of all the alternatives should be assessed. It has not been discovered what exactly in the 6PPD/6PPD-quinone structure causes Coho pre-spawn mortality.

The U.S. Tire Manufacturing Association (USTMA) provided comments and initial thoughts regarding the selected chemicals (USTMA, 2021. Appendix A). These comments indicate that other PPDs have the potential to be similar in performance to 6PPD. Although not ideal from a health perspective due to other concerns, it may be that other PPDs would be preferable to 6PPD

if they are shown not to cause pre-spawn mortality in Coho salmon, even though all the PPDs assessed in this memo were ranked very high for aquatic toxicity and high for persistence. If further studies confirm that Coho pre-spawn mortality is unique to 6PPD-quinone, other PPD compounds could be acceptable substitutes to reduce negative impacts to Coho salmon until a safer alternative is developed. However, given the numerous hazard concerns with PPD molecules, they are not an ideal long-term solution for anti-ozonant activity in tires.

Of the chemicals assessed in this report, all were scored as BM-1 ("Avoid: Chemical of High Concern") except for 77PD, TMQ, ethoxyquin, and dilauryl thiodipropionate. Of these, 77PD is most likely to be a suitable replacement for 6PPD, since it is also a member of the PPD class of chemicals. However, comments from the USTMA suggest that it would not provide sufficiently long-lasting protection in tires, and may need to be combined with other chemicals. Similarly, ethoxyquin has shown promise in the past as an anti-ozonant, but was phased out due to less effectiveness compared to 6PPD. Further research is required to determine if there are situations or combinations where these chemicals may have acceptable performance as anti-ozonants compared to 6PPD.

USTMA comments on TMQ and dilauryl thiodipropionate indicate that they do not have sufficient performance to replace 6PPD as the main anti-ozonant in tires, though they may be useful as part of a mixture to increase the performance of other compounds. TMQ is currently used in this role as a co-antiozonant/antioxidant with 6PPD. Dilauryl thiodipropionate is used as an antioxidant to protect the synthetic polymers as the chemical plant before use in tire manufacturing.

There may be additional chemical alternatives we have not investigated. There are some examples of tires in use today that presumably do not use 6PPD as an anti-ozonant, where the chemicals used for this purpose are not publicly known. 6PPD is a staining compound, so tires that do not mark would not be able to include 6PPD. These include non-marking tires used on equipment such as indoor forklifts. In addition, there are some examples of white tires that meet all regulations to be road legal,[5] which also presumably do not use 6PPD because it would change the color of the tires. Airless tires (i.e., non-pneumatic tires) are currently in development, which would use much less or no rubber, as only the tread would potentially contain rubber—the sidewall would not. Airless tires are not available yet in passenger cars, but are in use in other applications like golf carts, military vehicles, and forklifts. Manufacturers are working on products for use in passenger vehicles.

When asked, industry experts did not know what anti-ozonants are used in these alternate tire types, but did express concern that they do not perform to the standard of other tires containing 6PPD. The composition of tires is considered proprietary information, so if this information is not shared publicly then we must test further to discover what anti-degradants are used and to compare performance.

[5] Example: https://www.cokertire.com/tires/36x4-firestone-non-skid-all-black-806031.html

Conclusion

The alternatives assessed showed a range of hazard scores. Many of them scored Benchmark 1 and would be considered regrettable substitutions. We also found a number of Benchmark 2 alternatives and one Benchmark 3 alternative, suggesting there may be opportunities for improvement. However, data gaps—particularly around transformation products and urban runoff mortality syndrome—make it difficult to determine whether any are safer than 6PPD, especially with respect to toxicity towards Coho salmon. We need to conduct more research to fill these data gaps and test more to investigate the feasibility of potential safer alternatives.

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Appendix A

October 8, 2021

Ken Zarker, Craig Manahan
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Re: Department of Ecology research on 6PPD and proposed alternatives to 6PPD

Dear Ken and Craig,

This letter is intended to provide the State of Washington Department of Ecology with additional information about the technical feasibility of several antioxidants and antiozonants currently being evaluated by the Department. We understand that the Department is currently conducting research in response to Washington Senate bill 5092 which provides $195,000 to the Department to "assess potential hazards of 6PPD (CAS 793-24-8) and other chemicals or chemical classes and breakdown products used as antioxidants and/or antiozonants in tires and submit a technical memo to the appropriate committees of the legislature by December 1, 2021."

We thank the Department for sharing the list antioxidants and antiozonants that will be assessed for their potential hazards. Alternatives to 6PPD must provide the same functions as 6PPD in a tire to ensure tire safety and performance. Several of the substances that are being assessed by the Department do not meet the needed functions to be considered as possible alternatives to 6PPD. Other substances that are being assessed by the Department lack enough information at this time to be considered as an alternative to 6PPD. Below is an overview of each of the antioxidants and antiozonants being assessed by the Department and additional information about whether these substances provide the needed functions to be considered an alternative to 6PPD.

USTMA and our members are committed to supporting an alternatives analysis of 6PPD in tires under the California Department of Toxic Substances Control (DTSC), Safer Consumer Products Regulations (SCPR). We encourage continued coordination and collaboration of the Department and DTSC on the alternatives analysis for 6PPD in tires under the SCPR.

I. Overview of the functions 6PPD provides in manufacturing safe and durable tires

6PPD is the most effective antioxidant and antiozonant and is utilized by all USTMA members. 6PPD reacts rapidly with ozone and can last the lifetime of a tire. The reason it can last until an 80,000-mile tire is worn out is that only part of it dissolves in the rubber when it is mixed into the rubber compound. The antiozonant migrates through the rubber to the surface during the operation of the tire where it forms a film. The film reacts with ozone, and as it is used up, more antiozonant moves to the surface. The dispersed but undissolved 6PPD in the rubber compound eventually dissolves as 6PPD is depleted (used up) and serves as a reservoir during the lifetime of the tire. If the migration of the

antiozonant is too slow, the tire will not be fully protected; if the migration rate is too fast, the antiozonant will be used up before the tire is worn out. It should also be noted that the oxidation products from 6PPD are also effective antioxidants/antiozonants although not as effective as 6PPD. This also contributes to the ozone protection provided during the life of the tire.

6PPD is also an antifatigue agent. Antifatigue agents reduce the degradation of the rubber compound that takes place during the flexing of the tire. Flexing builds heat, which causes degradation. Underinflated tires cause excessive flexing and high heat buildup, which can lead to unsafe conditions. In 2014 it was reported that 7 out of every 10 vehicles had at least one underinflated tire.[1] In addition to providing protection against ozone, 6PPD will also greatly reduce the rate of reaction of the rubber with oxygen in the atmosphere.

Thus, alternatives to 6PPD must also meet these critical functions and have the following qualities:

- Continuously present at the surface of the tire to ensure protection of the rubber compound from degradation due to oxygen and ozone;
- Adequate solubility and diffusivity in rubber compounds;
- Reactive with ozone but not too reactive in order to prevent premature depletion;
- No adverse effects on the rubber processing;
- Available in rubber compound over a tire's entire life cycle to ensure protection of the rubber;
- Low toxicity of the material and any transformation products; and
- No adverse effects on tire safety and performance.

II. Antioxidants and antiozonants that are being evaluated by the Department of Ecology

A. Substances that do not provide the critical functions necessary to be considered an alternative to 6PPD

1. CCPD, CAS number 4175-38-6

CCPD is also a member of the PPD class of chemicals. Thus, this material may have the potential to form a quinone and it is unknown if other PPD substances cause the same impact on coho salmon. CCPD is not considered a safer alternative to 6PPD as this material would not be expected to provide the lasting protection needed to protect the rubber compound through a tire's useful life. This material is similar to 77PD in that it migrates through the rubber faster than 6PPD and is expected to only provide 1-2 years of protection from oxygen and ozone.

2. IPPD, CAS number 101-72-4

IPPD is also a member of the PPD class of chemicals. Of all of the chemicals in the PPD class, IPPD has been shown to show the highest level of skin sensitivity and therefore is not considered a safer alternative to 6PPD. As a member of the PPD family, this substance also has the potential to form quinone and it is unknown if other PPD substances cause the same impact on coho salmon.

[1] https://www.tirereview.com/rma-70-vehicles-underinflated-tires/

3. TMQ 26780-96-1

This is used in tire compounds today as a co-antiozonant/antioxidant with 6PPD. By itself, it has been shown to have only 52% of the activity of 6PPD. By itself, it does not provide sufficient antiozonant protection to the rubber.

4. 6QDI 52870-46-9

This is an oxidation product of 6PPD and has the same carbon framework. It has been shown to be both an effective antiozonant and antioxidant, but its chemistry on aging produces 6PPD, and thus the 6PPD quinone would be produced from tires containing this material.

5. NBC 13927-77-0

This compound would be expected to act as an antiozonant, but would render the compound very difficult if not impossible to process in a tire plant. Additionally, it contains the heavy metal nickel. Some of the warnings listed include the following:

- May cause an allergic skin reaction [Warning Sensitization, Skin]
- Causes serious eye irritation
- May cause allergy or asthma symptoms or breathing difficulties if inhaled
- Suspected of causing cancer [Warning Carcinogenicity]
- May cause long lasting harmful effects to aquatic life

6. Dilauryl thiodipropionate 123-28-4

This compound is used as an antioxidant to protect synthetic polymers made in a chemical plant until they are used in a tire plant. It is expected to have little, if any antiozonant activity.

B. Substances where there is not enough information to be considered an alternative to 6PPD

1. 77PD, CAS number 3081-14-9

77PD is a member of the PPD class of chemicals. 77PD does not meet the critical functions needed to be a safer alternative to 6PPD as 77PDA migrates through rubber faster than 6PPD and thus it provides a shorter period of protection than 6PPD. Research conducted in the 1950's demonstrates that the use of this material in combination with other stabilizers in high ozone areas was shown to have effective protection against oxygen and ozone for only 1-2 years.[2] It is unclear how long the protection would last in a modern tire. It may be possible to combine this material with other members of the PPD family for longer tire life, but this would take extensive tire testing and research. Equally important is the fact that as a member of the PPD family, it would be expected to form a quinone like 6PPD. To date, it is unknown if other chemicals in the PPD family will form a quinone and whether they would cause the same impact on coho salmon.

[2] "Weather aging of elastomers on military vehicles" W. England, J. Krimian and R. Heinrich, Rubber Chemistry and Technology, (1959) 32 (4): 1143–1154.

2. 7PPD 3081-01-4

7PPD is a member of the PPD class of chemicals and is extremely similar to 6PPD in chemical structure. There is only a one carbon difference in the two structures. It would be expected to be an excellent antiozonant, an excellent antioxidant, an excellent antifatigue agent, migrate at approximately the same rate as 6PPD, but also form a quinone very similar to 6PPD.

3. Ethoxyquin 91-53-2

This compound was an early candidate for tires in the 1950's and was used in some tires during that period. In early studies, it was shown to be 87% as effective as 6PPD in the initial reaction with ozone. The migration rate is not known, so it is unclear how long protection would last. It is classified as mildly to moderately toxic. The by-products of ozonation have not been fully characterized, and their toxicity is unknown.

III. USTMA welcomes the opportunity for continued engagement with the Department on the assessment of potential hazards of 6PPD and other antioxidants and antiozonants

USTMA thanks the Department for their continued engagement with USTMA on this important issue. We recognize the importance of filling relevant data gaps on 6PPD-quinone as expeditiously as possible. We look forward to meeting on October 12th with the Department and researchers from the University of Washington and the Washington Stormwater Center to review relevant data gaps and to discuss efforts underway to fill critical data gaps.

Thank you again,

Sarah E. Amick

Sarah E. Amick
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