Saving coho salmon: Alternatives for 6PPD in tire manufacturing

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Land acknowledgement

We recognize that UC Berkeley sits on the territory of xučyun (Huichin), the ancestral and unceded land of the Chochenyo speaking Ohlone people, the successors of the sovereign Verona Band of Alameda County. This land was and continues to be of great importance to the Muwekma Ohlone Tribe and other familial descendants of the Verona Band.

We recognize that every member of the Berkeley community has, and continues to benefit from, the use and occupation of this land, since the institution's founding in 1868. Consistent with our values of community, inclusion and diversity, we have a responsibility to acknowledge and make visible the university's relationship to Native peoples.

It is vitally important that we not only recognize the history of the land on which we stand, but also, we recognize that the Muwekma Ohlone people are alive and flourishing members of the Berkeley and broader Bay Area communities today.

Partner acknowledgements

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1   Executive summary

Coho salmon populations support ecological systems and are a focal species among indigenous populations along the Northern Pacific Rim, of which are currently listed at endangered species. In early 2021, 6PPD-quinone, which is a transformation product of 6N-1,3-dimethylbutyl-N-phenyl-p-phenylenediamine (6PPD), was discovered as the cause of prespawn mortality in Coho salmon in the Pacific Northwest.[1]

6PPD is a critical tire rubber additive due to its high-performing antidegradant properties. Due to its demonstrated ecotoxicity, we are aiming to identify chemical alternatives to 6PPD that not only uphold technical functionality, but also minimize human health and environmental hazards. We have identified four strategies that will be outlined in the text of this report. Each of which will be subject to a comparative technical assessment, as well as a comparative human and environmental health and performance assessment.

Our first strategy involves synthetic modification of the 6PPD molecule in order to prevent formation of its toxic quinone form. Our second strategy proposes implementation of a class of synthetic food preservatives called gallates, as these have yet to be explored as tire antidegradants. Our third proposed strategy involves implementation of lignin, which is second most abundant plant-based polymer in the world, into the tire rubber formulation as an antidegradant. Lastly, our fourth strategy involves a broader process-level changes, including adjustments to vulcanization processes schemes and rubber formulation.

This report aims to assess baseline technical feasibility and as to how environmental and human health performance compares to 6PPD. Rigorous testing will need to be conducted in order to fully and comprehensively assess as to whether any of the proposed replacement or replacement schemes can meet the same performance standards of 6PPD.

2 Introduction

Rubber tires are among the most ubiquitous consumer products in industrialized society, finding use across much of the transportation industry, including in automobiles, airplanes, and bicycles. Though commonplace in this sense, the ubiquity of tires belies the degree to which tires are highly engineered to achieve a stringent set of technical performance metrics to ensure consumer safety and tire longevity. Critical to achieving maximal lifetime performance is a tire's ability to withstand chemically and mechanically harsh environments. This particular need spawned a significant research enterprise in the mid to late twentieth century in order to develop additives that would stabilize the rubber matrix and protect it from degradation throughout its lifecycle, including production, storage, and perhaps most importantly, its use as a product. From a chemical standpoint, these additives serve to protect rubber polymers from participating in radical chain reactions with various reactive species, including but not limited to surface oxygen and ozone, as well as carbon radicals that can form within the matrix of the tire itself. Macroscopically, these reactions manifest as cracking and degradation in the tire, reducing lifespan and introducing myriad health and safety concerns. The need for effective tire antidegradants is certainly great.

While a number of compound classes have been considered as tire stabilizing agents over the years, phenylenediamines (PPDs) provide particularly effective protection against oxygen and ozone degradation in tires. Chief among these, N-1,3-dimethylbutyl-N-phenyl-p-phenylenediamine (6PPD) became a popular choice as an antidegradant among tire manufacturers beginning in the 1970s due to its superior performance as an antiozonant and its ability to terminate radical chain reactions that occur as the result of mechano-oxidative stress within the tire itself. In addition to its technical performance, the synthesis of 6PPD is relatively straightforward and inexpensive, both of which are attractive from the standpoint of industry stakeholders. Indeed, according to current manufacturing practices, each of the ten to fifteen rubber materials that comprise a tire contains some amount of 6PPD, such that 6PPD has become as ubiquitous as tires themselves.

Despite its presence in a common consumer product, 6PPD was relatively unknown to all but industry specialists until recently.

2.1 Coho salmon and the discovery of 6PPD quinone

In the 1990s the city of Seattle, Washington and other local municipalities were conducting extensive physical and biological restoration of the lower Puget Sound. These activities included removing culverts and other impassable barriers for fish, the placement of large woody debris and gravel substrate, the removal of noxious weeds, and the planting of native vegetation. One metric that was to be used to mark the success of these restoration efforts was to evaluate the extent to which adult salmon would return to spawn in the newly improved habitats.[2] The early monitoring efforts, conducted from 1999-2001 identified an unusual condition in coho salmon returning to restored sites to spawn.

> Affected coho spawners observed in post-restoration effectiveness monitoring surveys showed a consistent suite of symptoms that included surface swimming, gaping, loss of equilibrium, and pectoral fin splaying. The onset of the syndrome was rapid, and stricken fish typically died within a few hours.[2]
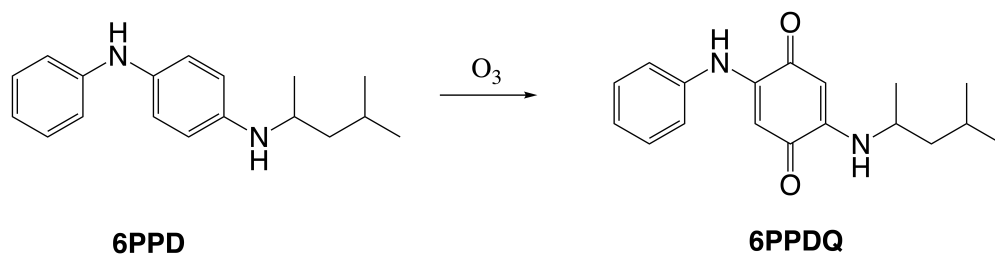
Figure 1: The ozonation of 6PPD results in the formation of 6PPDQ, which has been identified as the primary toxicant responsible for the mass die-off of coho salmon.[1]

The phenomenon, known as pre-spawning mortality (PSM), was confirmed by a near-total retention of eggs in female carcasses inspected during the surveys conducted by NOAA Fisheries with assistance from Washington Trout and Seattle Public Utilities.[3]

Coho salmon are anadromous fish. They hatch in freshwater streams and spend a year in streams and rivers then migrate out to the ocean to feed and grow before returning to the streams to spawn and then die. They are found throughout the North Pacific Ocean and in most coastal streams and rivers from Alaska to central California.[4] Pacific salmon are keystone species - they play an immense role in maintaining the health and prosperity of the various ecosystems they live in throughout their lives. They are an important food source for both terrestrial and aquatic predators as well as release important nutrients back in the environment after they spawn. Due to the dynamic nature of their life-cycle, pacific salmon are estimated to have significant relationships with over 130 wildlife species.[5] In addition to their ecological importance, salmon also hold significant cultural importance to many indigenous communities across the Pacific Northwest where they are an important species for ceremonial, subsistence, and commercial purposes for local tribes.[6]

Coho salmon populations are at a fraction of what they used to be, with Central California coho salmon populations estimated to be at 1% of their 1940s levels.[7] With multiple coho populations listed as endangered or threatened under the Endangered Species Act, trying to understand the mechanisms of which urbanization has played on salmon populations has been the focus of many years of research. Previous studies have shown urban stormwater runoff can be toxic to aquatic species. Motor vehicles release a range of chemicals into the environment as a consequence of tire and brake pad wear, leaking oil and transmission fluid, and tailpipe exhaust. These contaminants accumulate on highways, streets, and other impervious surfaces and are then mobilized into stormwater runoff and make their way into local waterways during rain events.[8] Stormwater runoff was long thought to be the cause of coho salmon PSM, however, absent definitive contamination identification, the toxicity and mode of action has been largely unknown.

This changed earlier this year when Tian, *et al.* published compelling results[1] that implicated the presence of 6PPD-quinone (6PPDQ), an ozonation product of 6PPD (Figure 1), in road runoff as the cause of acute mortality in coho salmon across the Pacific Northwest ($LC_{50} = 0.79 \pm 0.16\,\mu g\,L^{-1}$). This work has led to several subsequent studies investigating 6PPD, its transformation into 6PPDQ, and the toxicity of both compounds to marine life. While the mechanisms of toxicity have not been fully elucidated, initial research suggests that 6PPDQ fatally disrupts the blood-brain barrier in coho salmon.[9] This type of toxicity

Table 1: Toxicity of 6PPD and 6PPDQ to various aquatic species. Among tested species, the toxicity of 6PPDQ to coho salmon presents the most worrisome result.

Species	6PPD	6PPD quinone
Coho salmon[a]	$LC_{50} = 250 \pm 60 \ \mu g \, L^{-1}$	$LC_{50} = 0.79 \pm 0.16 \ \mu g \, L^{-1}$
Chum salmon[b]	Not toxic	Not toxic
Zebrafish[c]	Delayed hatching rates, reduced body size, spinal abornamlities at $137 \, \mu g \, L^{-1}$	Not toxic at $137 \, \mu g \, L^{-1}$
Japanese medaka[c]	80% mortality rate at $107 \, \mu g \, L^{-1}$	Not toxic at $107 \, \mu g \, L^{-1}$
Water flea[c]	100% mortality rate at $138 \, \mu g \, L^{-1}$	Not toxic at $138 \, \mu g \, L^{-1}$
Amphipod[c]	100% mortality rate at $286 \, \mu g \, L^{-1}$	Not toxic at $286 \, \mu g \, L^{-1}$

a

b

c

has been demonstrated to be unique to coho salmon, and has not been observed in closely-related chum salmon.[10] Another study[11] found that the parent compound 6PPD introduces varying degrees of acute and chronic toxicity in other aquatic species, including zebrafish, Japanese medeka, water flea, and amphipod.

Beyond aquatic species, exposure to 6PPD also raises human health concerns. It as it has been empirically shown to cause skin sensitization,[12] meaning that it may induce a dermal allergic response in susceptible individuals. Other health concerns include skin and eye irritation, and potential developmental effects if a developing embryo or fetus are exposed to levels of the compound over the established regulatory limit.[13] Various authoritative entities, such as the GHS framework adopted by both Korea (NCIS) and Japan,[14] also corroborate the study findings of 6PPD as an acute aquatic toxicant. Additionally, the functional compound is additionally classified as being bioaccumulative per the Canadian Environmental Protection Agency Environmental Registry Domestic Substances list (OECD).

The newly discovered toxicity of 6PPD and 6PPDQ poses a significant problem in a material economy that relies on the manufacture and use of tires across all sectors.[5] Alternative rubber formulations that maintain tire performance and longevity while addressing the recently discovered health and environmental impacts associated with 6PPD are necessary, and the need for these solutions will only become more severe if and when government entities begin to regulate the use of 6PPD in tire manufacturing. This report begins to address this need by presenting a number of potential strategies for minimizing or eliminating the use of 6PPD in tire production. Our strategies are varied in scope, ranging from proposed "drop in" chemical antidegradants, to reconsidering fundamental aspects of rubber manufacturing processes. Applied individually or in concert, these approaches open the possibility for a more sustainable future across the lifecycle of tires.

2.1.1   Cultural significance of coho salmon

Identifying 6PPDQ is a significant discovery in terms of water contaminants that salmon are exposed to in urban waterways, but we would like to emphasize that 6PPDQ is not the only threat to Coho salmon survival. For example, there are invasive species that prey on salmon, dam infrastructure that blocks access to estuaries and freshwater streams and overharvesting.[15]

Indigenous tribes and First Peoples represent a demographic that has been systematically discriminated against and disenfranchised. Coho salmon have a cultural significance for various tribes along the Northern Pacific Rim.[6]

Some of the tribes based in, what is now known as, British Columbia: Council of the Haida Nation, Nuxalk, Tsimshia, Kw'alaams; Puget Sound - Seattle, Washington: Lushoot-seed people; Oregon and California: Columbia River Inter-Tribal Fish Commision including the Nimiipuu, Umatilla, Yurok; are all examples of indigenous groups that have historical and cultural ties to Pacific salmon.[15]

Pacific salmon, including the Coho, feed First Nations/ indigenous communities, but are also a key element to spirituality. First Nations who depend on Pacific salmon for fishing, depend on salmon to continue a legacy of stewardship to the land. The named tribes, along with many other Federally and non-Federally acknowledged tribes depend on coho salmon for ceremonial, subsistence, and commercial purposes. Pacific salmon play a major part in tribal and individual identity, connection to the natural land, and are often the focus of stories of origin, and cultural ceremonies. While sourcing an alternative to 6PPD is a unique opportunity to promote ecological sustainability; this effort coincides with preserving indigenous practices of the many First Nations whom which depend on.

2.2   The chemical function of 6PPD

6PPD has enjoyed wide use in the tire manufacturing industry for over half a century due to its ease of production, its low cost, and its ternary function as an antiozonant, antioxidant, and antifatigue agent to protect tires from catastrophic degradation. While the most attractive replacements to 6PPD would exhibit similar or improved performance along each of these metrics, any viable substitute must protect tire rubber from all three classes of degradation while minimizing or eliminating the deleterious environmental effects of 6PPD and its derivatives as outlined in Section 2.1. As such, understanding both each of these three breakdown pathways and the mechanisms of 6PPD's action to mitigate them proves critical to the process of eliminating 6PPD in tire manufacturing. Much of the work in this section follows the presentation of Huntink[16] and the references therein.

2.2.1   Degradation pathways in tires

Tires are highly engineered consumer products comprised of a number of different material layers. The majority of these layers consist of various rubber compounds that serve the mechanical functions of the tire. Both natural and synthetic rubbers are used in tire manufacturing and consist of unsaturated hydrocarbon polymers networked together with sulfur cross-linkages. A non-exhaustive set of constituent monomers is presented in Figure
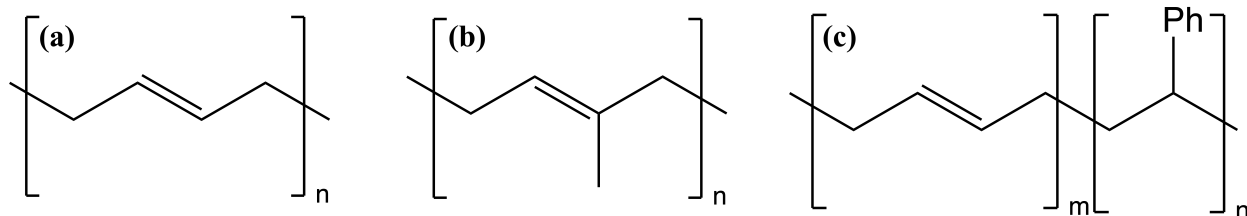
Figure 2: Selected monomers used in compounding the following rubbers: (a) polybutadiene, (b) polyisoprene, and (c) polystyrene-co-butadiene. All monomers possess degrees of unsaturation that are vulnerable to chemical degradation during tire production and use.
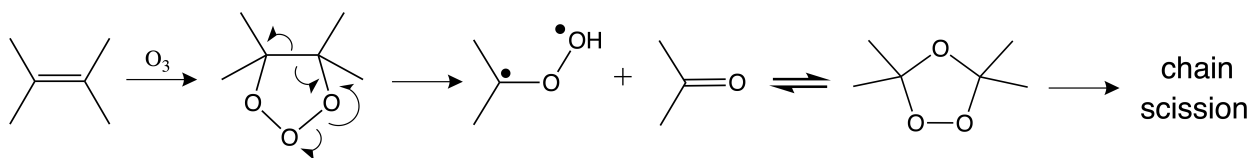
Figure 3: Standard mechanism for alkene ozonolysis that leads to surface degradation of polymer networks in tires at ozone concentrations as low as a few pphm. Chain scission leads to surface cracking and tire failure. Figure adapted from Ref. 16.

2. While a full discussion of the structure of these polymers is outside the present scope (although see Sec. 7), aspects of the molecular features of rubber the molecular structure of these rubbers introduces susceptibility to chemical and mechanical degradation. Specifically, unsaturated olefins throughout the rubber network are vulnerable to attack by ozone and various free radicals that are present in and around the tire.

Degradation due to ozone.   The surface degradation of tires due to ozone spurred a significant research effort by the U.S. government that led to the discovery of PPDs as antiozonants. Degradation due to ozone results in discoloration and severe cracking at the surface of the tire, leading to a breakdown in tire performance and safety. Tropospheric ozone attacks sites of unsaturation at the surface of the rubber, following the standard mechanism of alkene ozonolysis (Figure 3).[17] This reaction proceeds even at concentrations in the parts per hundred million (pphm) range, which are achieved or exceeded in both unpopulated and highly urban environments, respectively,[18] posing a severe problem for tire performance across all end-use applications. Ozone exposure can also degrade polymer networks through attack on the sulfur cross-links within the rubber, although this reaction proceeds more slowly than alkene ozonolysis and thereby provides less source for concern.[19]

Degradation due to carbon radicals.   The presence of carbon radicals within the matrix of the tire provides another source of mechanical failure in tires. As with ozonolysis, degradation due to carbon radicals proceeds through the attack of olefins within the tire; however, this breakdown typically occurs due to the creation of carbon radicals within the tire itself, rather than environmental exposure to these species. The mechanical effects of this chemical failure differ based on the particular formulation of the rubber, leading to either hardening or softening depending on the polymeric composition. In any case, the pro-

Initiation

RH $\xrightarrow[\text{shear}]{\triangle T}$ R• + H•

R-R $\xrightarrow[\text{shear}]{\triangle T}$ 2 R•

R• + O$_2$ $\longrightarrow$ ROO•

Propagation

ROO• + RH $\longrightarrow$ R• + ROOH

ROOH $\longrightarrow$ RO• + OH•

ROOH + RH $\longrightarrow$ ROH + R• + H$_2$O

RO• + RH $\longrightarrow$ ROH + R•

OH• + RH $\longrightarrow$ HOH + R•

Termination

ROO• + R• $\longrightarrow$ ROOR

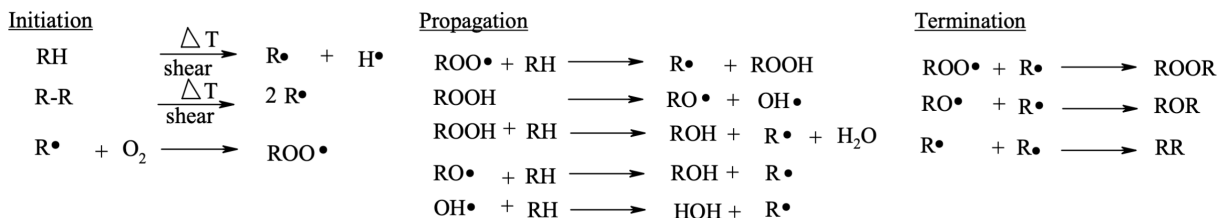RO• + R• $\longrightarrow$ ROR

R• + R• $\longrightarrow$ RR

Figure 4: Radical chain reactions of rubber polymers that occur within tires. Propagation of both carbon and oxygen radicals degrades the rubber network, leading to critical tire failure. Figure adapted from Ref. 16.

liferation of carbon radicals within the tire destroys the polymer network that is necessary for the mechanical function of tires.

Carbon radicals are introduced into the tire compound through homolytic cleavage of carbon–carbon and carbon–hydrogen bonds within the rubber polymers (Figure 4).[20] Over the course of manufacture and during their end-use in vehicles, tires are exposed to high temperatures and large shear forces, which causes mechanico-chemical cleavage of bonds in the rubber and the creation of free carbon and hydrogen radicals; this source of free radicals is particularly relevant in tire manufacturing. This cleavage can also occur through exposure of the tire to ultraviolet (UV) light,[21] although this breakdown can be mitigated through the introduction of chromophores. Once present, these radical species initiate a radical chain reaction that can further destroy the polymer network within the tire, leading to mechanical failure .

Degradation due to oxygen radicals. Oxygen radicals pose a similar but distinct source of the chemical breakdown of the polymers within rubber compound. Multiple proposals for the mechanism of oxygen radicals have been put forth, and it is likely that each of these contribute to the formation of oxygen radicals. First, upon exposure to molecular oxygen, carbon and hydrogen radicals present in the tire (see preceding paragraphs) may produce highly reactive peroxy radicals (Figure 4). In addition to this, trace amounts of peroxide that are introduced in tire manufacturing may also be present and catalyze rubber oxidation.[22, 23] Even in small quantities, these impurities can both initiate and propagate the radical chain within the tire. Regardless of their origin, peroxy radicals within the rubber contribute to the chemical and mechanical failure of tires. Conjugated olefins are particularly susceptible to this form of attack.

2.2.2 6PPD as an antidegradant

While the use of a number of antidegradants has been explored over the course of the most recent half century have been explored, none exhibit the same performance as 6PPD. Specifically, unlike other alternatives, 6PPD is highly potent and protect tires from each of the three sources of chemical and mechanical breakdown as outlined in Sec. 2.2.1 above. Different molecular features of 6PPD contribute to its reactivity towards ozone and carbon and oxygen radicals, and some aspects of this chemistry remain ill-understood. Nevertheless,

much is known about the action of 6PPD as an antidegradant, and this knowledge should guide research into alternatives.

6PPD as an antiozonant.   At least two mechanisms are known to contribute to 6PPDs action as an antiozonant.[24,25]

The first and most obvious of these is through the preferential reaction of 6PPD with surface ozone. Acting as a so-called "kinetic scavenger," 6PPD effectively depletes the ozone concentration at the surface of the tire, minimizing the ozone exposure of the vulnerable olefins within the rubber polymers.[26] Despite the ability to react with ozone more rapidly than rubber olefins, the volatility of 6PPD and similar compounds prevents long-term protection of the rubber through a scavenging mechanism: once at the surface of the tire, 6PPD may evaporate before it can react with and consume reactive ozone. The surface concentration of 6PPD in the tire is partially replenished as molecules diffuse to the surface of the tire, but this is not sufficient to overcome 6PPD depletion through reaction with ozone or evaporation from the tire surface. Indeed, computational models of kinetic scavenging that take these features into account fail to predict the extent to which 6PPD protects tires from surface ozonation.[27] This result indicates alternative mechanisms also contribute to 6PPD's protection against ozone damage.

While not entirely understood, 6PPD is also known to form a film at the surface of the tire that provides a mechanical barrier to prevent ozone exposure at the surface of the tire.[28] This protection is similar to that afforded by coating rubbers with various waxes,[29,30] however the film formed by 6PPD exhibits persistence where wax-based films do not. This is likely due to the ability of the 6PPD film to regenerate over the lifetime of the tire. The molecular features of 6PPD that lead to film formation are not well characterized, but it is known to consist of 6PPD and its transformation products, rather than ozonized rubber.[28] Importantly, not all structurally similar PPDs form these protective films. Nevertheless, studies into the relative antiozonant performance of these compounds indicate that the 6PPD film formation contributes critically to its function as an antiozonant in tires. Though 6PPD functions as an antiozonant through both scavenger and film-forming mechanisms.

6PPD as an antioxidant and antifatigue agent   While carbon and oxygen radicals degrade the rubber in tires through different mechanisms, these breakdown pathways are fueled by an interconnected radical chain reaction. 6PPD is able to prevent rubber oxidation due to both peroxy and carbon radicals through termination of this unified radical chain. While consumption of both classes of radicals will serve to terminate chain propagation, elimination of catalytic peroxy radicals is the most critical feature of antioxidant performance, particularly under the conditions of tire production.[16] Similar to other diarlyamines, 6PPD acts as an antifatigue agent through an H-abstraction mechanism that consumes free peroxy radicals. This process ultimately forms nitroxyl radicals, which further quench the radical chain through their reaction with alkyl radicals.[31] Vulcanization partially reverts remaining 6PPD nitroxyl radicals back to 6PPD molecules, which may then function to consume additional peroxy radicals and further protect the rubber in the tire. A summary of the reactions illustrating the antioxidant and antifatigue chemistry of 6PPD can be found in Figure 5. These complementary reaction pathways help to explain 6PPD's highly efficient
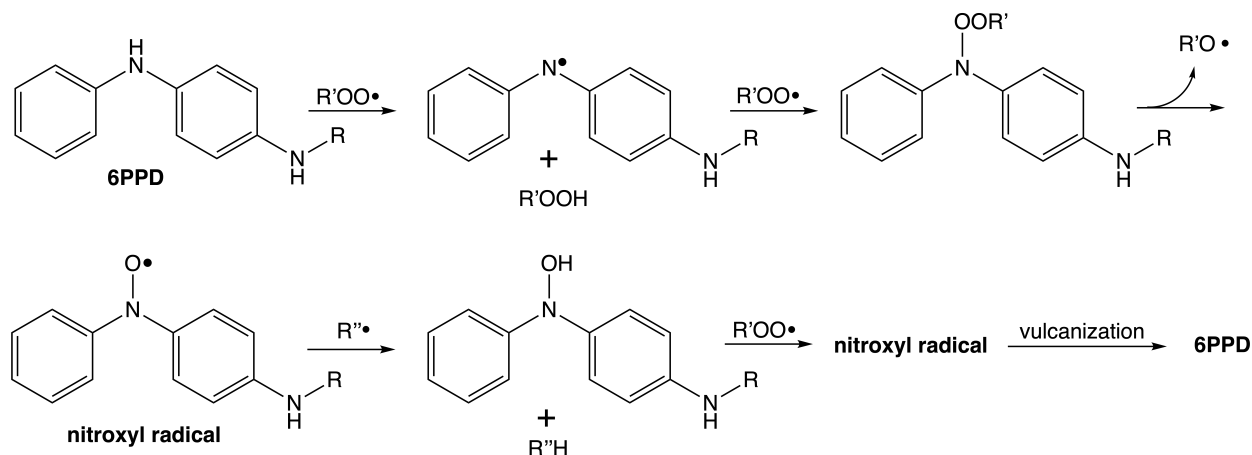
Figure 5: Chemical basis for the action of 6PPD as an antifatigue agent in tires. 6PPD consumes highly reactive peroxy radicals (R′OO·) to form a nitroxyl radical that can then absorb macroalkyl radicals (R″·) that also damage tires. 6PPD is partially regenerated during vulvanization, and these recovered molecules further stabilize the tire from oxidate damage. Adapted from Ref. 16.

performance as an antioxidant.

2.2.3   Chemical features of 6PPD alternatives

At least two pathways to eliminate 6PPD from tire manufacturing exist: (1) identifying alternative compound(s) that achieve the same chemical performance as 6PPD and (2) engineering rubber to be inherently less susceptible to the forms of degradation outlined above. In what follows below, we present strategies of the first kind in Sections 4, 5, and 6; we examine the possibility of alternative rubber formulations in Sections 7. While we present a complete description of our approach in Section 3 below, some comments of the molecular features of potential 6PPD replacements are warranted at present. This brief discussion will assume that the target alternative is a single, drop-in compound, although the possibility that different compounds may be substituted into different tire compounds depending on the degradation pathway of concern should not be discounted. In order to protect against surface ozonation, a compound must of course exhibit reactivity towards ozone that exceeds that of the rubber compounds themselves. The ideal compound would also persist on the surface of the tire, in contrast to 6PPD and related antiozonants that are too volatile to provide long-term protection for the tire in the absence of film formation. Should a similarly volatile antiozonant be identified, it is critical that this compound form a protective film similar to 6PPD in order to protect the rubber over the lifetime of the product. Replacement compounds must also protect the rubber from fatigue and oxidation due to the presence of peroxy and carbon radicals throughout production and use of the tire.

3   Approach

3.1   Project Scope

The scope of this project is to investigate a range of functional chemical alternatives to 6PPD in tires. We are seeking an alternative that will minimize ecological toxicity while maintaining the antidegradant and antiozonant capacities vital to tire performance, so as not to compromise the technical and safety specifications. Target compounds are to be evaluated through comparative assessments for both chemical hazard and technical performance. While there are numerous different types of tires ranging from passenger vehicle tires to airplane tires, our assessment does not focus on one specific tire type.

   This document is intended to evaluate a range of functional chemical alternatives to 6PPD in tires through a comparative chemical hazard assessment and a comparative technical performance assessment of all chosen alternatives. This document is not meant to provide the feasibility of these potential alternatives from a technical perspective (resulting tire durability and safety) as we do not have the resources to conduct these experiments.

3.2   Technical Criteria

A viable replacement for 6PPD must function both as an antiozonant and an antioxidant in order to uphold function as an antidegradant. In addition, it must feasibly be incorporated into tire infrastructure, the tire manufacturing process, and match or exceed performance standards as established by the U.S. Tire Manufacturer's Association (USTMA) and safety standards as established by the National Highway Traffic Safety Administration (NHTSA) in the Federal Motor Vehicle Safety Standards (FMVSS).

   Various metrics need to be considered when evaluating tire performance. Given the project scope and available resources, we are unable to directly measure many of these properties. We have, however, identified some surrogate physical and chemical properties that we hope will guide the search for 6PPD replacements. For the purpose of this project, we are taking what these surrogate properties represent as necessary for our 6PPD replacement, but recognize that they are in no way wholly sufficient to determine a candidate compound's success as an alternative because of the nuanced technical requirements of tires.

   That being said, a 6PPD replacement should be reactive towards oxygen and ozone. To assess oxygen reactivity, we will use the redox potential of a substance. This will serve to predict a compounds tendency to give up electrons in the oxidation process and react with the oxidative species that are implicated in the tire degradation process.

   Identifying a surrogate to assess a compounds reactivity with ozone is more difficult. Since different researchers assess this in different ways, the measurement of ozone reactivity may vary from strategy to strategy. An explanation on how those numbers are being used will be included in each strategy.

3.3   Human and environmental health criteria

In the hazard assessment component of this project, the hazards of all candidate alternative were assessed using methods adopted from the GreenScreen® for Safer Chemicals (Green-

Figure 6: Health and environmental hazard table color-coding scheme

Screen) framework, developed by Clean Production Action, which is a publicly available and transparent chemical hazard assessment method that has been designed to promote the adoption of greener and safer chemicals.[32] To ensure that our comparative hazard assessment is fully comprehensive and reflects the current state of the science, our general process in acquiring hazard information specific to each of the evaluated alternatives is as follows: (1) collecting hazard information with authoritative lists from Pharos project,[33] which summarizes hazard, use, and exposure information from authoritative lists, (2) compiling data using cursory literature reviews in GoogleScholar and PubMed, (3) screening data compiled by the European Chemical Agency (ECHA), followed by (4) predictive modeling using EPA CompTox Chemicals Dashboard[34] and quantitative structure–activity relationships (QSAR) computational modeling systems for predicting various types of toxicities.[35]

Many of the authoritative lists maintained by various countries are based on category criteria of the Globally Harmonized System for Classification and Labeling (GHS). Hazard data was also acquired from Material Safety Data Sheets (MSDS) and administrative reports. We assessed 15 endpoints in human health (Group I and II endpoints), and 2 endpoints related to environmental fate and toxicity. Please note that Group II and Group II* imply that the health endpoints in each group are implicated with a singular exposure and with repeated exposures, respectively. The applicable abbreviations and definitions from each of these endpoints is provided below.

In order to conduct a *comparative* health hazard assessment, it is necessary to standardize the data relating to each of these endpoints so that they are relative to one another, and allow for a holistic picture as to how each alternative compares to 6PPD and its quinone form so that a regrettable substitution is not to be selected as the alternative. The hazard level classification system was primarily adopted from the The GreenScreen Chemical Hazard Critera (Section I) of the GreenScreen® for Safer Chemicals document for the purpose of this project. Similarly, the Material Health Assessment Methodology developed by the Cradle2Cradle Products Innovation Institute, which provides a framework for the assessment of material and chemical hazards and risks for products being assessed by the Cradle to Cradle Certified™ Products Program,[36] was also used for this hazard classification process. The Hodge-Sterner index, which gives a ranking of 1 through 6 from "Extremely toxic" to "Relatively harmless" based on LD50 value, was also employed for interpreting and standardizing acute mammalian toxicity data in the literature.[37]

The processes outlined in these various frameworks were adopted for the purpose of this comparative hazard assessment in standardizing data and designating hazard levels of each chemical for each endpoint as being: very high, high, medium, or low. In instances where there may be conflicting hazard data between authoritative lists and in the scientific literature, the most conservative hazard level was applied. Hazard levels have additionally been color-coded in this assessment according to the color-scheme provided in Figure 2.

We then assessed the confidence level of hazard scores as high or low after evaluating

the reliability of the various data sources. For the purpose of this comparative hazard assessment, a hazard score is said to have high confidence if information came from an authoritative lists. A score received low confidence if data was conflicting or incomplete, or if the only data available were from using in *in silico* QSAR modeling. Endpoints in which the data is said to be low confidence are indicated by *italicized* hazard ratings in the comparative health and environmental performance hazard table (Appendix I). In accordance with the Cradle2Cradle Material Health Assessment framework, QSAR modeling methods were only used for endpoints of aquatic toxicity (both chronic and acute), bioaccumulation, and persistence when other data was not available.[36] QSAR modeling results for other endpoints, such as the Group I human health endpoints, were considered insufficient.

Both 6PPD and 6PPDQ have known and potential human and environmental health hazards that range from moderate to high across Group I and II/II* endpoints (Table 2). These hazards represent the hazard baseline against which we compare each alternative strategy chemical in more detail in the sections below. In terms of health and environmental health performance, our minimum criteria for a safer substitute for 6PPD are (1) not posing any additional human health hazards for known Group I and Group II/II* endpoints compared to 6PPD and 6PPD-quinone and (2) minimal environmental toxicity, especially acute aquatic toxicity, and low levels of persistence.

Table 2: Toxicity endpoints used for hazard assessments. Descriptions obtained from Ref. 33

Group I Human Endpoints

Carcinogenicity	Ability to cause cancer or contribute to the development of cancer
Mutagenitcity	Ability to cause or increase the rate of mutations, which are changes in genetic material in cells.
Reproductive Toxicity	Ability to disrupt the male or female reproductive systems, changing sexual development, behavior or functions, decreasing fertility, or resulting in loss of the fetus during pregnancy.
Developmental Toxicity	Ability to cause harm to the developing child including birth defects, low birth weight and biological or behavioral problems that appear as the child grows.
Endocrine Activity	Ability to interfere with hormone communication between cells, which controls metabolism, development, growth, reproduction and behavior (the endocrine system).

Group II and II Endpoints

Acute mammalian toxicity	Ability to be fatal on contact, ingestion, or inhalation for humans and other mammals.
Systemic Toxicity	Ability to cause specific, non lethal but serious damage on contact or ingestion or inhalation, to one or more organs, such as the heart, lungs, liver, etc. distant from the point of entry of the toxicant.
Neurotoxicity	Ability to cause damage to the nervous system including the brain.
Skin sensitization	Ability to trigger allergic reactions on the skin.
Respiratory sensitization	Ability to result in high sensitivity such that small quantities trigger asthma, rhinitis or other allergic reactions in the respiratory system.
Skin irritation	Ability to cause irritation or serious damage to the skin.
Eye irritation	Ability to cause irritation or serious damage to the eye.

Ecotoxicity

Aquatic Toxicity acute/chronic	The intrinsic property of a substance to be injurious to an organism in a short-term, aquatic exposure to that substance, or in relation to the life-cycle of the organism
Terrestrial ecotoxicity	Ability to cause harm to land based plants, animals or microorganisms.

Fate

Persistence	The length of time the chemical can exist in the environment before being destroyed (i.e., transformed) by natural processes.
Bioaccumulation	Accumulates in organisms concentrating as it moves up the food chain.

Physical Hazards

Flammability	Easily ignited and capable of burning rapidly.
Reactivity	May spontaneously ignite or explode on its own or in contact with water.

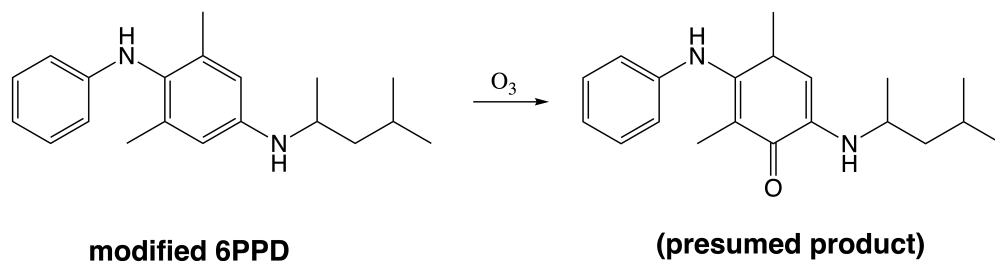**modified 6PPD**　　　　　　　　　　**(presumed product)**

Figure 7: Proposed methylated 6PPD and presumed reaction product upon exposure to ozone. Modification of 6PPD prevents the formation of 6PPDQ upon ozonation.

4 Modification of 6PPD to mitigate toxicity

The many functions of 6PPD and the technical requirements of tires make the process of eliminating 6PPD use in tires a formidable challenge. A basic implication of the structure-function principle in chemistry suggest that compounds that are structurally similar to 6PPD should achieve similar functions. It is therefore reasonable to begin the search for alternatives to 6PPD by considering modified versions of 6PPD, which are likely to exhibit similar chemical and physical properties. This approach is a double-edged sword in that compounds structurally similar to 6PPD and 6PPDQ would also be expected to exhibit similar toxicity. Still, it may be possible to identify designer molecules that engineer away the toxicity of 6PPD and its derivatives while preserving its antidegradant properties. Unlike our other approaches to removing 6PPD from tire manufacturing (*vide infra*), this strategy proceeds through identification of alternative chemical structures that likely do not yet exist. As such, empirical data for both the technical and environmental performance of modified versions of 6PPD are not available. Additionally, a number of modifications to the structure of 6PPD can be envisioned, and this large scope of alternatives renders experimental testing of all possible candidate molecules intractable. In lieu of an empirical evaluation of modified versions of 6PPD, computational predictions of chemical function provide an alternative, high-throughput approach to screening the activity potential antidegradants toward ozone and oxygen and carbon radicals. We begin by motivating one particular class of modifications to 6PPD before providing an overview of the extant computational quantum chemistry frameworks that may be used to evaluate the performance of these candidates *in silico* (Section 4.1). We continue with a discussion of the environmental implications of this approach (Section 4.2) before concluding this section with a brief summary of this strategy.

The antiozonant properties of 6PPD stem in part from its reaction with ozone through an aryl diamine moeity. Acting in this way, each unit of 6PPD is able to scavenge multiple units of ozone by forming byproducts that are also active against ozone.[16] One of the stable final products of this series of ozonation reactions is 6PPDQ, the toxicant of primary concern in the context of this study. In this way, the function of 6PPD as an antiozonant is directly linked to its environmental toxicity. Modification of 6PPD such that 6PPDQ does not form as a final ozonation product could improve the environmental outcomes of this antidegradant significantly while retaining at least some of its function as an antiozonant.

We can imagine modifying the substituent ortho to the aryl amine in 6PPD in order to obtain one class of compounds that may achieve this balance of preserving technical
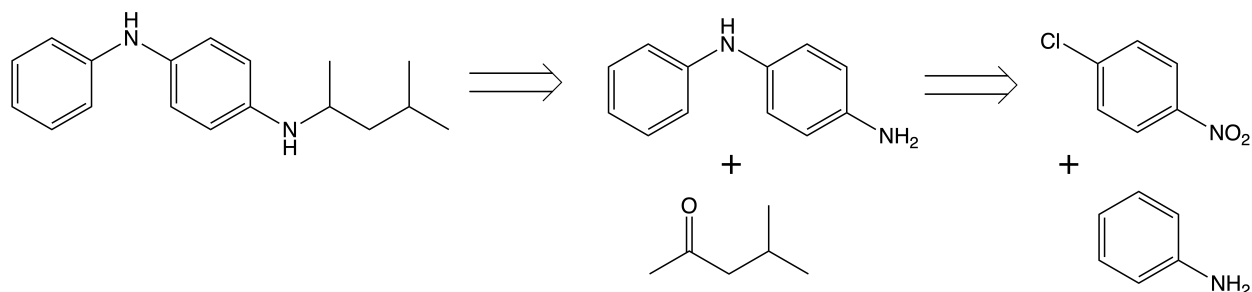
Figure 8: Industrial retrosynthesis of 6PPD. Modified versions of 4-chloronitrobenzene that would be necessary to synthesize modified 6PPDs are not commercially available.

performance while mitigating environmental harms. As indicated in Figure 7 replacement of the R = H group in 6PPD with an alkyl chain would prevent the formation of 6PPDQ. Conceptually, the simplest substitution would be R = CH_3, although alterations with longer and more complicated side chains can be envisioned. Regardless of the side chain, this route of structural modification necessarily diminishes the amount of ozone that can be consumed by each molecule of antidegradant by effectively poisoning one of its reactive sites. Still, such modifications are not expected to diminish the reactivity of the (more reactive) sites ortho to the alkyl amine, which can still consume at least one molar equivalent of ozone to form the monocarbonyl indicated in Figure 7. Furthermore, the rate of reaction with ozone is generally considered to be more important than the number of molar equivalents of ozone that an antidegradant can consume,[16] and we do not expect such modifications to significantly influence the rate of the initial reaction with ozone.[38]

It should also be noted that modified 6PPDs may be more difficult to obtain synthetically. The standard industrial synthesis of 6PPD begins begins with the reaction of 4-chloronitrobenze and aniline to form 4-amino-diphenylamine, which is then reacted with methyl-isobutyl ketone to afford 6PPD (Figure 8). Each of these precursors is commercially available and relatively cheap. Alkylated versions of 4-chloronitrobenzene, which would be necessary for the synthesis of the modified versions of 6PPD suggested above laong the same pathway, are not commercially available. Additionally, the presence of bulky alkyl groups on modified 4-chloronitrobenzene may obstruct reaction with aniline in the primary step of the industrial synthesis of 6PPD. Synthetic concerns notwithstanding, modified 6PPDs represent a potential drop-in substitute that would prevent the leaching of 6PPDQ in the environment, should they exhibit the necessary technical requirements as antidegredants.

4.1 Technical performance of modified 6PPDs

As noted, data on the technical performance of 6PPDs as indicated above is limited, where it exists at all. Computational screening of the reactivity of these compounds provides an attractive and efficient alternative to synthesis and empirical testing of a large number of candidate replacements. While this screening has not been completed in the present work, we summarize the relevant chemical literature and provide recommendations for a future evaluation procedure.

The use of computational tools to understand and predict the reactivity of antidegradants

in tires dates at least to the late 1960s, when Furukawa, *et al.* used Hückel theory to correlate frontier orbital energies with oxidation potentials across a series of antioxidants, including a number of PPDs.[39] These authors note that the computed oxidation potential of such compounds reports on their capacity to act as both antioxidants and antiozonants in rubber compounds. While important at the time, this early work reports only crude correlations between theory and experiment, a reflection of the state of the art of computational chemistry half a century ago. In the intervening decades, a number of advances in both quantum chemistry and computational technology have paved the way for establishing a significantly improved protocol for evaluating oxidation potentials as a proxy for reactivity towards active oxygen species. These theoretical and practical advances have yet to be fully applied to the problem of identifying antioxidants and antiozonants in tires, and doing so represents a powerful opportunity to achieve high throughput screening of alternatives to 6PPD.

The continuing development of orbital-based density functional theory (DFT)[40] certainly represents the most significant advance in chemistry technology as it concerns study of the reactivity of organic molecules similar to those used in the present context. Modern density functionals are able to efficiently predict reactivity in these systems with high fidelity, among many other things improving our ability to compute oxidation potentials *a priori*. Indeed, recent studies have found that orbital energies obtained from DFT correlate with experimental potentials across a diverse set of molecular structures exceptionally well (RMSD = $70\,\text{mV}$–$83\,\text{mV}$; $R^2 > 0.99$).[41,42] Explicit evaluation of the complete thermodynamic cycle associated with reduction and oxidation reactions using DFT provides an even higher degree of accuracy (MAD = $56\,\text{mV}$; $R^2 > 0.998$), albeit at somewhat greater computational cost.[43] Further work that is currently in press reports the development of machine learning corrections to these potentials that brings theoretical and experimental results into even closer agreement.[44] Most of these computational schemes to determine oxidation potentials for small to medium organic molecules can be performed even on personal computers, and supercomputing technologies provide the opportunity to use high throughput screening across many systems of increasing complexity.*As such, computational determination of oxidation potential represents an attractive method for initial, coarse-grained examination of a wide array of 6PPD surrogates, including those obtained through the modifications suggested above.

After the completion of an initial screening based on oxidation potentials, more sophisticated computational tools can predict the specific reactivity towards ozone and various free radical species. Once again, advances in DFT make the prediction of reaction barrier heights that allow for theoretical determination of kinetic data tractable for molecules of the size under present consideration.[40] Molecular dynamics simulations can even begin to incorporate the effect of the rubber matrix on the performance of antidegradants, and work to this effect has been completed for a series of phenolic antioxidants in natural rubber by Lu, *et al.*[46] Extension of this work to include reactivity toward ozone will significantly aid

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*While outside of the scope of the present work, recent efforts to improve so-called semi-empirical Hamiltonian (SEH) methods for the prediction of oxidation potentials have also been relatively successful.[45] While extraordinarily cost-effective, even state-of-the-art SEH methods are a factor of two to three times less accurate than (uncorrected) results obtained using moderate density functionals.[41,43] In the opinion of the present authors, the reduction in computational time associated with SEH methods does not make-up for their reduced accuracy.

the identification of a 6PPD replacement.

4.2   Health and environmental performance of modified 6PPDs

Modified versions of 6PPD like those indicated above will prevent the formation of 6PPDQ, which is known to be acutely toxic to coho salmon even in exceedingly low concentrations.[1] By eliminating the production of this toxicant, these drop-in replacements address the most significant known concern associated with the use of 6PPD in tire formulations. Nevertheless, the environmental safety of these substitute compounds remains unknown, and it is difficult to predict whether these or their derivatives possess toxicity to coho salmon or other important aquatic species without experimental data to this effect, especially as the molecular origin of 6PPQ's toxicity is unknown. Due to the similarity of these structures to those of 6PPD and their novelty within the chemical manufacturing industry, we expect computational toxicology and QSAR models to be of limited help in evaluating the safety of these specific modified 6PPDs. Inasmuch as these novel compounds are likely to possess the safety hazards associated with all PPDs and related compounds (See Refs. 47, 48 and references therein) they do not represent a solution that is sustainable in the long-term. Still, such compounds may serve as a temporary stopgap measure that addresses the most significant toxicological impacts associated with current antidegradants. In any case, experimental determination of the aquatic toxicity of modified 6PPDs is a necessary precursor to their industrial implementation.

4.3   Summary of modified 6PPDs as alternative antidegradants

Modified versions of 6PPD represent the most attractive alternative to 6PPD in terms of their potential to be used as an immediate drop-in replacement. They are expected to exhibit similar function to 6PPD in the tire due to their similar structure. These similarities are particularly important to the protective film that 6PPD derivatives form on the surface of the tire, as this film formation is not well understood and may be difficult to replicate with alternative antidegradants. Following some computational screening procedure, it is imperative that robust ecological assays of effective compounds and their derivatives on coho salmon and other species be performed prior to large scale implementation. As these compounds are not found in nature, they possess more *a priori* risk than the other strategies detailed below, and they may not be advisable for this reason.

5 Gallates as a replacement additive

5.1 Background information

Gallates are a class of antioxidants that are added to food products, specifially those containing fats and oils, to extend shelf life and/or prevent rancidity due to oxidation. They find importance in both human and animal feed, because they help conserve the nutritional properties of foods. There is a wide variety of antioxidants amongst this class that are both of natural and synthetic origin.

The overlapping functionality of the antioxidant compounds used in the food industry and in other products, such as building materials, cosmetics, and notably, rubber, is not new. Ethoxyquin was originally developed by the rubber industry as an antidegradant. Due to its high antioxidant efficiency and stability, it has been further developed for use as a preservative in animal feed and dehydrated forage crops, as an anti- scald agent in pears and apples, and a color preservative in spices.[49] While use of ethoxyquin has been suspended due to technical infeasibilities and a long list of negative human and environmental externalities, the historic overlap of these industries is an encouraging precedent for the use other classes of antioxidants, namely *gallates*, antidegradants in tires.

The gallates are characterized by their phenolic core and pendant carboxylic acid, which can be derivatized with various groups to construct this family of molecules(Figure 9). The modularity of the core compound gives access to many compounds with a broad range of physical properties. This range makes the gallates a tunable alternative to the use 6PPD in tires.

R = nPr, iPr, nBu, iBu, nPent, iPent
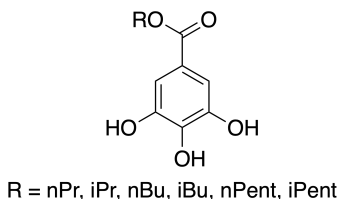
Figure 9: Generalized structure of a gallate compound

5.2 Technical performance of synthetic food preservatives

There is no literature directly comparing compounds from the gallate family to 6PPD with respect to antioxidant and antiozonant activity. Therefore, redox potential (E_h) will serve as a proxy for a reaction with singlet oxygen where the antioxidant is required to be a strong enough reducing agent to afford antidegradant properties. Additionally, activity toward ozone will be exemplified through studies on the reaction of ozone with biological systems that are treated with a gallate compound for protection.

Squella et. al. reported that the half-wave redox potentials of gallate compounds with both branched and linear side chains from propyl to pentyl range from $0.49\,\text{V}$–$0.51\,\text{V}$ calibrated against an Fe/Fe^+ redox couple as a quasi-reference electrode.[50] 6PPD has a half-wave redox potential of $-0.12\,\text{V}$ against the same quasi-reference electrode, indicating it is

a stronger reducing agent than the range of gallates tested. Still, the gallate compounds tested have a redox potential below that of singlet oxygen (0.8 V), suggesting that the tested gallates could adequately quench reactive oxygen species that could lead to degradation of the tire.

With respect to antiozonant activity, two studies on biological systems suggest that propyl gallate specifically is able to protect from damage due to reaction with ozone. In a report by Thompson and Pauls, a microsomal membrane was treated with ozone and was found to have lost 51% of its phospholipid content compared to a control experiment, indicating significant degradation of the membrane. When a microsomal membrane in a solution treated with propyl gallate was exposed to ozone, only 38% of the phospholipid content was lost compared to the control.[51] In a study by Rangappa et. al., corn seedlings were fumigated with ozone five days after emergence and the dry weight of the corn produced by such seedlings was reduced by 36% compared to a control that was not fumigated with ozone. In an experiment where the soil in which the corn was growing was treated with propyl gallate, the dry weight of the corn produced was reduced by only 25% compared to a control that was not fumigated with ozone or treated with propyl gallate.[52] Both of these studies suggest that propyl gallate is capable of providing protection against ozonative damage. A thorough study of this compound in a rubber matrix would be necessary to understand the full potential of its antioxidant and antiozonant properties and how they compare to 6PPD.

In order for a gallate compound to perform its antidegradant functions, it needs to diffuse to the surface of the tire where it can react with oxidants. If an antidegradation compound diffuses too slow, it may not be able to adequately protect the surface of the tire from oxidation and ozonation. If it diffuses too quickly, the antidegradant may be consumed too quickly and decrease the lifetime of the tire.

To date, there are no publications on the diffusivity of a gallate compound through a rubber matrix. Instead, the chemical properties that may affect diffusivity, such as molecular weights (MW) and octanol-water partition coefficients ($\log K_{ow}$) were evaluated to qualitatively compare the gallates to 6PPD (Table 3).

Based on these metrics, gallate compounds and 6PPD are likely to diffuse through rubber at a similar rate. The molecular weights of the gallates are similar to that of 6PPD. While the octanol-water partition coefficients suggest the gallate compounds are slightly more hydrophilic than 6PPD, it is not clear that the octanol-water media will be representative of a rubber matrix, so it is not clear how much, if at all, this will affect the diffusivity. Importantly, the syntheses of gallate compounds allow for variability in the length and identity of the group off of the carboxylic acid moeity (i.e. n-propyl, n-butyl, n-pentyl). When one increases the length of this chain to six (hexyl) or seven (heptyl) carbon atoms, both the molecular weight and the partition coefficient becomes more like that of 6PPD, likely making the diffusivity more similar as well. Thus, should the diffusivity of a gallate compound be unsatisfactory, that diffusivity can be easily tuned to meet the performance standards for the tire by modulating the chain length.

5.3   Health and environmental performance of food preservatives

Table 3: Comparison of the octanol-water partitioning coefficient of 6PPD and select gallates.

	MW $(\mathrm{g\,mol^{-1}})$	K_{ow}
6PPD	268	4.68
n-propyl gallate	212	1.80
n-butyl gallate	226	2.40
n-pentyl gallate	240	2.70

| Common Trade Name | Group I Human Endpoints | | | | | Group II and Group II* Endpoints | | | | | | | Ecotoxicity | Fate | | Physical Hazard | |
	Carcinogenicity	Mutagenicity	Reproductive Toxicity	Developmental Toxicity	Endocrine Activity	Acute mammalian toxicity	Systemic toxicity	Neurotoxicity	Skin sensitization	Respiratory sensitization	Skin irritation	Eye irritation	Aquatic Toxicity Acute/chronic	Persistence	Bioaccumulation	Reactivity	Flammability
Parent Compound																	
6PPD	DG	DG	DG	H-M	DG	M	DG	DG	H	DG	M	M	vH	L	vH	DG	DG
6PPD quinone	DG	DG	DG	DG	DG	DG	DG	DG	DG	DG	DG	DG	vH	DG	DG	DG	DG
Strategy: Food additives/preservatives																	
Propyl gallate	L	L	L	L	M	M	DG	DG	H	DG	M	H	vH	L	vL	L	L
Octyl Gallate	L	L	L	DG	M	M	DG	DG	H-M	DG	M	DG	H	L	L	L	L
Lauryl gallate	DG	DG	DG	DG	L	L	M	DG	H-M	DG	M	H	H	H	L	L	L
Epigallocatechin gallate	DG	L	M	DG	DG	M	DG	DG	H	DG	M	H	H	vH	L	L	L
Gallic acid	L	L	L	DG	DG	L	L	DG	M	DG	H	H	L	L	vL	L	L

Figure 10: Lignin comparative human and environmental hazard table

For the purpose of the hazard assessment, the following gallate and gallate-like molecules have been selected for comparison to 6PPD and 6PPDQ: propyl gallate, octyl gallate, lauryl gallate (also known as dodecyl gallate), gallic acic, and epigallocatechin/epigallocatechin gallate. The full comparative human and environmental hazard assessment for gallates relative to 6PPD and 6PPDQ is presented in Figure 5.

Propyl gallate is a food additive used to prevent oxidation of foods containing fats and oils. It has been deemed not carcinogenic and not genotoxic according to the EU Panel on Additives and Products or Substances used in Animal Feed (FEEDAP).[53] However, recent reviews from the European Food Safety Authority (EFSA) found that propyl gallate exposure does pose potential concern as an endocrine disruptor.[54] Additionally, Propyl gallate is irritant to skin and eyes and a dermal sensitiser.[53] Inhalation of propyl gallate may also pose respiratory hazards, though health endpoints related to this exposure route have not been adequately characterized at this time. Propyl gallate's insolubility in water makes it a comparatively better candidate to replace 6PPD than some of the other chemicals on this list. There are conflicting regulatory opinions about propyl gallate's aquatic toxicity, as it is classified as GHS Hazard code H410 by the European Union (EU) Manufacturer REACH hazard submissions as being potentially very toxic to aquatic life with long lasting effects.[55] Predicted acute toxicity values (96-hr LC50) using QSAR positions propyl gallate to have a *moderate* rating, as corroborated by the USEPA.[56] The more conservative classification has been applied for the purpose of the comparative hazard table.

Octyl gallate is another type of food preservative and is reported to possess antifungal activity against *Saccharomyces cerevisiae* and *Zygosaccharomyces bailii*. The fungicidal activity associated with octyl gallate is due to its ability to act as a nonionic surface-active agent (surfactant).[57] Results of *in vivo* animal bioassays evaluating the carcinogenic or mutagenic potential of octyl gallate have not yielded any positive results, nor have any *in silico* methods. Octyl gallate was not found to affect endocrine receptor activity in the experimental system used by Amadasi et al.[58] There is some evidence that it can inhibit 5α-reductase and thus influence androgen regulation[59].[60] The EFSA has established a No-Observed-Adverse-Effect-Level (NOAEL) of $50\,\mathrm{mg\,kg^{-1}}$ bodyweight-per-day for reproductive toxicity endpoints based on one animal bioassay,[61] though this is several of orders of magnitude lower than NOAELS for known reproductive toxicity endpoints. More data is likely needed to make a truly conclusive assessment regarding potential reproductive toxicity, and the implications of octyl gallate exposure on this health endpoint therefore need to be investigated more thoroughly at a wider range of doses and in additional types of experimental models. Octyl gallate has been shown to cause acute mammalian toxicity in only very high, non-environmentally relevant doses,[62] though it has been classified as being acutely toxic to mammalian species through oral routes of exposure by GHS hazard codes (H302). There is currently inadequate literature on the acute/chronic aquatic toxicity of octyl gallate, though *in silico* methods have alluded this endpoint may be of concern and therefore renders the need for experimental data.

Relative to the more studied types of gallates, there is limited data available on lauryl gallate, as indicated by the data gaps for the various (primarily Group 1) human endpoints, though it has been shown that lauryl gallate does not present endocrine activity,[59] has been shown to have low acute mammalian toxicity, and though not shown experimentally, is unlikely to raise concern for genotoxicity.[63] Lauryl gallate's classification in regards to aquatic

toxicity is based on the Canadian Environmental Protection Act (CEPA) Environmental Registry of Domestic Substances List (DSL), which has flagged lauryl gallate as being inherently toxic in the environment based on QSAR-derived LC50 values for fish and other aquatic species.[64]

Epigallocatechin and Epigallocatechin gallate are plant-derived phenolic compounds such as epigallocatechin gallate are found in a wide variety of plant species and are regarded for their anti-inflammatory/antioxidant properties associated with their consumption. A compound of interest is the catechin (-)-epigallocatechin-3-gallate, which is a naturally occurring phenolic compound found in green tea leaves. There is Limited data is available on their bioaccumulation and toxicity effects, though an animal bioassay has provided evidence of potential reproductive toxicity and/or endocrine disruption at very high dosages (85 mg/kg in rats).[65] Further, the Denmark EPA has classified both epigallocatechin and (-)-epigallocatechin-3-gallate as potentially causing skin reactions upon dermal exposure.[66] This agency has additionally raised concern that this compound may have mutagenic properties based on QSAR modeling, though it has been shown in the literature that this is unlikely.[67] Other hazards, including those related to aquatic toxicity (H401) are based on GHS hazard codes.

Within the Group I human health endpoints, Gallic acid does not pose carcinogenicity, mutagenicity, or reproductive toxicity hazard concerns. It additionally poses low concern for systemic toxicity and acute mammalian toxicity,[68] though according to the New Zealand Hazardous Substance and New Organisms (HSNO) Chemical Classifications, it may be implicated in skin and eye irritation.[69] Gallic acid, which has not been classified as an aquatic toxicant based on GHS codes, showed demonstrably low aquatic toxicity in the literature as well (LC50 ¿ 100 mg/L).[70]

In summary, there still exists inconsistencies in the types of health and environmental performance endpoints for which we have data on, and the confidence levels of that data. For example, all environmental fate data for this class of compounds was obtained from the EPA CompTox Chemical Dashboard; the classifications (all of which are *low*, as presented in Figure 5, are based on *prediction* only. At minimum, the comparative hazard assessment which we have conducted indicates which of the selected gallates may present more viable alternatives than others, and which would need to undergo additional testing to obtain more sound experimental data.

6 Lignin as a replacement antioxidant

6.1 Background Information

Lignin is the second most abundant plant-based polymer in the world after cellulose. It makes up about one third of the material in the cell walls of plants.[71] It is a by-product of the paper and pulp industry where about 98 % of this lignin waste is either burned or sent to a landfill.[72]

The physical and chemical properties of lignin depends on which plant the lignin is coming from and the extraction process. Lignin is a very complex polymer with phenolic functionality and is a great candidate for use in tires due to its high abundance, antioxidant properties, thermal stability and cost-competitiveness.

6.2 Technical performance of lignin

Similarly to the gallates, little work has been devoted to directly comparing the antioixdant/antiozonant performance of 6PPD with lignin in rubber media. Thus, the intrinsic chemical properties of redox potential (E_h) and rate of reaction with ozone will be used to assess the feasibility of replacing 6PPD with lignin.

Karnaouri et. al. reported that the half-wave redox potentials of a range of lignin compounds derived from birch and spruce wood ranged from 0.31 V–0.33 V calibrated against an Fe/Fe^+ redox couple as a quasi-reference electrode.[73] Comparatively, 6PPD has a half-wave redox potential of -0.12 V against the same quasi-reference electrode, indicating that 6PPD is a stronger reductant than the range of lignin compounds tested in the Karnaouri report.[74] Nevertheless, both the lignin compounds and 6PPD are capable of reducing singlet oxygen, which has a redox potential of 0.8 V. This suggests lignin is capable of protecting a tire from oxidative degradation.

Manly and Mbachu reported on the degradation of lignin by ozone and studied the kinetics of the transformation by monitoring the consumption of ozone. They found using a variety of lignin sources that the rates of consumption of ozone by the samples ranged from 0.11 mmol–12.0 mmol O_3/C_9 unit lignin/minute.[75] Because the molecular weight of a lignin sample is not precisely defined in $g\,mol^{-1}$, as in a small molecule like 6PPD, but instead in terms of carbon units, it is not appropriate to compare rates of ozone consumption between lignin and 6PPD. However, these rates suggest there is promising reactivity between ozone and lignin compounds that could potentially translate to antidegradation capabilities for lignin. Separate tires each infused with either 6PPD or lignin would need to be exposed to ozone to compare the antiozonation properties of each compound directly.

There is no published work on the diffusivity of lignin through rubber media. Therefore, the chemical properties that affect diffusivity, such as molecular weights (MW) and octanol-water partition coefficients ($\log K_{ow}$) were evaluated to qualitatively compare lignin to 6PPD. (Table 6.2).

Lignin is likely to diffuse through a tire slower than 6PPD. The range of molecular weights of lignin compounds is an order of magnitude larger than that of the small-molecule 6PPD. The size of the compound will affect diffusivity, as heavier molecules generally diffuse slower in polymeric media. The octanol-water partition coefficient for lignin indicates that lignin

Table 4: A comparison of the 6PPD and Lignin diffusivity properties.

	MW ($\mathrm{g\,mol^{-1}}$)	K_{ow}
6PPD	268	4.68
Lignin	5000 – 5600	-0.57 – -1.09

is far less hydrophobic than 6PPD.[76] Regardless of the media through which the compound is diffusing, a difference in the hydrophobicity of two compounds will affect the rates of diffusivity for those two compounds based on different degrees of intermolecular interaction between the compound of interest and the media. While 6PPD and lignin have different diffusivity properties, it is possible that the lower volatility of lignin will accommodate a slower diffusion rate by maintaining a higher concentration of lignin on the surface of the tire for a longer period of time. Additionally, it may be possible to modulate the molecular weight of the lignin compounds to achieve a lower molecular weight polymer, which will diffuse faster.

The use of lignin as a rubber filler and antioxidant has been well studied. However, few studies have been conducted to directly compare lignin's performance in tires with currently used tire antioxidants such as 6PPD. One study by Nilmini and Surej in 2019 directly compared two common tire antioxidants, 6PPD and sterically hindered styrenated phenol (SP), with Kraft Lignin (KL), which is derived from wood pulp. The study used a variety of combinations of 6PPD, SP, and KL, as well each compound individually in SBR rubber test samples and tested for specific strength metrics. Then the samples were aged for 70 h at 70 °C and retested. Comparing the sample that exclusively contained KL and the sample that exclusively contained 6PPD, comparisons between the two antioxidants can be made. Specific metrics that were tested include tensile strength, tear strength, abrasion resistance, percent hardness improved and flex fatigue. Tensile strength measures the ability of the rubber to resist breaking when stretched; tear strength measures resistance to tearing; abrasion resistance is a measure of how much rubber is lost from the surface of the sample due to friction of an abrasive surface; percent hardness is indicative of ability for the rubber to resist surface scratching; and flex fatigue is the number of cycles required to produce cracks in the rubber sample. In the 6PPD and KL sample, the concentrations of 6PPD and KL was two parts per hundred rubber (phr). Of these metrics, KL outperformed 6PPD in all categories except for flex fatigue prior to aging (Table 5). After aging (Table 6), however, KL under-performed compared to 6PPD in all areas except for percent hardness improved, but only under-performed by slight amounts. Where KL failed to perform was in flex fatigue. In this particular measure, the 6PPD rubber sample resisted cracking for 60,000 cycles, where the KL rubber sample resisted cracking for only 8,000 cycles. Since tires must perform to very high safety standards, this particular measure is very important for safety and for longevity of the tire. However, there may be ways to increase the performance of lignin with regard to flex fatigue, such as combining it with other compounds or using different types of lignin. Since lignin performed well under every other metric tested, there is a possibility that lignin could be used as a replacement for 6PPD in tires if the flex fatigue issue could be solved.[77]

Another study conducted compares IPPD and TMQ, existing rubber antioxidants, with lignin/silica (L/S) and calcium lignate/calcium silicate (CL/CS). While these particular

Table 5: Comparison of 6PPD and lignin rubber compounds prior to aging.

	Tensile Strength (MPa)	Elongation at break (%)	Tear Strength (N mm^{-1})	Abrasion Loss (mm^3)	Crack Initiation (cycles)
6PPD	14.34	344	36.32	119.1	60000
Lignin	14.93	358	41.59	116.4	8000

Table 6: Comparison of 6PPD and lignin rubber compounds after aging.

	Tensile Strength (MPa)	Elongation at break (%)	Tear Strength (N mm^{-1})	Abrasion Loss (mm^3)	Crack Initiation (cycles)
6PPD	12.68	269	31.94	129.2	45700
Lignin	12.52	234	26.54	122.8	7000

antioxidants are not 6PPD, both are commonly used as SBR rubber antioxidants. IPPD is slightly less stable and blooms more than 6PPD where TMQ is often used in combination with 6PPD for maximum antioxidant and protection properties. This study, similarly to the study discussed above, adds a variety of different antioxidant concentrations to SBR rubber samples prior to aging them and testing for specific performance metrics. The metrics tested include tensile strength, which is the strength the sample can withstand when pulled apart; elongation at break, which measures overall flexibility of the rubber prior to breaking; thermal stability, measured by finding the temperature at which degradation begins (T_i) and ends (T_f); property retention when aged at a temperature of 90 °C for 7 d; and cross-link density, which enhances the durability of the rubber, to a certain extent (Table 7). Overall, the study concludes that the thermal stability of lignin/silica and calcium lignate/calcium silicate rubber samples exceeded that of the TMQ and IPPD samples. Regarding tensile strength, elongation at break, and cross-link density were all higher with the lignin/silca and calcium lignate/calcium silicate mixtures than IPPD and TMQ. Furthermore, the lignin derived antioxidants were more effective at retaining properties after aging than TMQ and IPPD. The presence of silica tended to enhance the antioxidant capabilities of lignin and the ideal concentration of the mix was found to be 8 phr. While the typical 6PPD concentration in a tire is 2 phr, the difference in concentration does not immediately make lignin a less viable alternative due to its low cost, abundance, and lack of toxicity compared to 6PPD.[78]

6.3   Health and environmental performance of lignin

Though there is substantially less toxicological data on lignin than our other proposed alternative, such as food additives, lignin is recognized as being intrinsically safe. The U.S. EPA has also evaluated lignin under the Safer Choice program and it is listed under the "Safer Chemical Ingredient List".[79] This has been verified by both experimental and modeled data, such as in an animal bioassay in which dermal administration of 0.1 and 0.5 g lignin compounds did not produce eye or skin irritation.[71] It has additionally been empirically shown that lignin holds anti-toxicant properties and may be able to be used in treatment of several

Table 7: Comparison of different aged properties of lignin/silica and calcium lignate/calcium silicate with IPPD and TMQ.

	Tensile Strength (MPa)	Elongation at break (%)	Ti/TF (°C)	Crosslink Density ($mol\,cm^{-3} \times 10^5$)
TMQ	13.9	875	291/664	7.3198
IPPD	13.41	900	268/665	7.5361
L/S	14.25	925	360/598	8.3988
CL/CS	15.16	950	354/725	9.355

health outcomes such as obesity, diabetes, thrombosis, viral infections and cancer.[80]

However, lignin is an incredibly complex and diverse polymer, and we recognize the difficulty in characterizing the human and environmental hazards of such a broad-reaching class of molecules. Due to the complexity of lignin, we have selected the three canonical monolignols which lignin if conventionally defined as being formed by for inclusion in our hazard assessment: (1) *p*-coumaryl alcohol, (2) coniferyl alcohol, and (3) cinapyl alcohol).[81] Please note that data surrounding these canonical monomers are extracted from laboratory MSDS sheets, implying that these are synthetic versions of the monomers that could be theoretically used to synthesize the polymeric version of this type of compound. It should not be implied that lignin degrades into these specific monomers.

The main hazards identified are related to respiratory irritation (which corresponds to the human health endpoint of "systemic toxicity"), skin irritation, and eye irritation as reported by GHS hazard codes[82][83][84]. Coniferyl alcohol and *p*-coumaryl alcohol monolignols have also been placed on an advisory list by the Ministry of Environmental of Denmark.[66] Because of the lack of toxicological data available, classification of this chemical as being potentially acutely toxic to mammalian species is based on QSAR modeling, and is therefore considered low confidence. A summary of the comparative hazard assessment across all health and environmental endpoints for the canonical monolignols and lignin relative to 6PPD and 6PPDQ is presented in Figure 4.

Common Trade Name	Group I Human Endpoints					Group II and Group II* Endpoints							Ecotoxicity	Fate		Physical Hazard	
	Carcinogenicity	Mutagenicity	Reproductive Toxicity	Developmental Toxicity	Endocrine Activity	Acute mammalian toxicity	Systemic toxicity	Neurotoxicity	Skin sensitization	Respiratory sensitization	Skin irritation	Eye irritation	Aquatic Toxicity Acute/chronic	Persistence	Bioaccumulation	Reactivity	Flammability
Parent Compound																	
6PPD	DG	DG	DG	H-M	DG	M	DG	DG	H	DG	M	M	vH	L	vH	DG	DG
6PPD quinone	DG	DG	DG	DG	DG	DG	DG	DG	DG	DG	DG	DG	vH	DG	DG	DG	DG
Strategy: Lignin																	
p-Coumaryl alcohol	DG	DG	DG	DG	DG	DG	M	DG	H	DG	H	H	DG	DG	L	L	L
coniferyl alcohol	DG	DG	DG	DG	DG	DG	M	DG	H	DG	H	H	DG	DG	DG	L	L
Sinapyl alcohol	DG	DG	DG	DG	DG	DG	M	DG	H	DG	H	H	DG	DG	DG	L	L
Lignin	L	L	L	L	L	L	L	L	L	L	L	L	L	L	L	L	L

Figure 11: Lignin comparative human and environmental hazard table

Though there is sparse data available regarding the human and environmental health endpoints of each of these monolignols and lignin as a polymer, both can be generally recognized as being benign and to not pose any imminent hazards to humans, aquatic life, or the environment. It should be noted, however, that though we have limited our comparative hazard assessment to these three monolignols, there are several other phenolic compounds that are expected to perform as lignin monomers in plants. Additionally, hazards associated with individual monomers may not necessarily be reflective of health endpoints related to lignin polymers, nor the transformation products of the lignin polymers depending on the context in which they are used and/or the environment they are subject to.

7 Alternative processes and formulations schemes

7.1 Background information

In the winter of 1839, Charles Goodyear discovered a process that would change the rubber industry forever; vulcanization. Vulcanization involves high temperature additions of sulfur to rubber to produce cross-links between rubber polymer chains. This chemical alteration of rubber prevents it from melting in high temperatures and from becoming brittle in low temperatures. Following Goodyear's discovery, rubber manufacturers continued to develop the process and its use in the rubber industry, as well as its importance, continues to this day.[85] Rubber vulcanization is a crucial step prior to the remaining manufacturing processes, such as mixing, calendaring, extrusion and curing. Mixing is a process in which rubber is mixed with various additives, including 6PPD. Calendaring is when steel or fabric is covered in rubber. Extrusion is a process where solid tire components are shaped. And finally, curing is the process of applying pressure and heat to give the tire its final shape.[86]

The high temperatures used during the vulcanization process require thermally stable antidegradants to protect the rubber from degradation during the vulcanization process and throughout the lifetime of the tire. Unfortunately, many naturally-derived antioxidants thermally degrade at vulcanization temperatures, and therefore cannot function as viable alternatives to thermally stable synthetic compounds, like 6PPD. This drastically limits the ability of the rubber industry to find alternative, less toxic, antioxidants to use in tires and other rubber products. If the temperature required to vulcanize rubber could be lowered, this would greatly expand the number of viable 6PPD alternatives for rubber formulations.

Apart from adjusting the vulcanization processes, adjusting rubber formulations may allow for use of rubber without 6PPD in tires. Hevea rubber, which is the most popular and widely-used natural rubber and makes up over 50 percent of tire formulations, can only be grown and processed in certain areas of the globe. In search of a domestically available source of natural rubber, researchers are investigating the use of dandelion rubber and guayule rubber for current rubber applications.[87] Since these alternatives do not have the same properties as hevea rubber, they require additives and completely different formulations, providing a unique opportunity to reformulate the tire with greener antioxidants. Two tire companies, Bridgestone and Continental, have created tires using guayule and taraxagum (dandelion derived) rubber, respectively. The formulations for these tires remain proprietary so determining which antioxidants are used is a challenge, however it is likely that 6PPD or a similar synthetic antioxidant is used.[87]

7.2 Technical feasibility of alternative

Since its development, vulcanization has been widely used across the rubber industry. Due to its effectiveness, this process is relied upon to create rubber products that are durable and applicable in many industries and applications. Efforts to increase the efficiency of this process are always ongoing in the rubber industry and are often focused on decreasing vulcanization times to increase rubber output. However, most importantly to the problem of replacing 6PPD is developing a vulcanization process that can occur at lower temperatures to accommodate thermally unstable antidegradants. Such antidegradants may have been
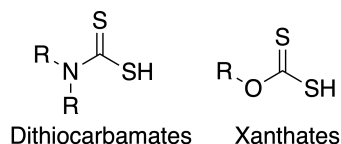
Figure 12: Generalized structures of a dithiocarbamate and a xanthate compound

viewed as unworkable in the past due to decomposition at vulcanization temperatures.

One way the rubber industry already increases the efficiency of the vulcanization process is through the use of accelerants. Accelerants are compounds that increase the speed or lower the temperature of vulcanization by either directly or indirectly assisting in the formation of the sulfur crosslinks between rubber polymers. Primary accelerants interact with the polymer chain directly to facilitate the formation of the sulfur crosslinks and are used in 0.5 to 1.5 phr dosages. Secondary accelerants are compounds used to activate the primary accelerants and are used in much lower concentrations than primary accelerants. Secondary accelerants significantly increase the speed of vulcanization, and should therefore be an area of focus for an investigation into low-temperature vulcanization processes for tires.

Currently, dithiocarbamates are one class of compounds used as secondary accelerators in tires. Research suggests that these accelerators are activated by nucleophilic attack on the dithiocarbamate carbon to form the precursors for cross-linking. Therefore, changing the electronics of the dithiocarbamate by using a xanthate instead may lead to faster activation of the electrophilic carbon and would enable lower vulcanization temperatures(Figure 12).[88] Xanthates are already used in the vulcanization of natural and synthetic rubber cements and adhesives (temperatures <120 ºC), but the extent to which they are used to lower the temperature of vulcanization of rubber for tires appears minimal.[89]

While vulcanization adjustments may prove to broaden the scope of viable alternatives to synthetic antioxidants, adjustments in the formulation of rubber compounds may also prove to be effective. Opportunities to change rubber formulations are arising as the search for alternatives to hevea natural rubber continue. Since much of the tire formulation revolves around the use of 6PPD, reformulation of the rubber compound in tires may be the only way to completely eliminate the need for this toxic antioxidant while maintaining performance requirements. The United States Department of Agriculture investigated the viability of using of guayule rubber in current rubber applications by studying how it can be modified to perform similarly to hevea. Since many of the superior properties of hevea rubber are thought to come from its non-rubber constituents like proteins, which guayule lacks, the USDA conducted an experiment on how the addition of amino acids affects guayule rubber's properties. During this study, amino acids proved to serve as effective antioxidants, significantly improving the thermal-oxidative stability of the rubber. The amino acids also served as plasticizers and cure accelerators, enhancing green strength. In particular, L-glutamine served most effectively as a plasticizer, antioxidant, and antireversion agent in guayule compounds.[90] In a follow up study, proteins were added to guayule rubber and proved to perform similar functions as amino acids, improving thermo-oxidative stability in almost all cases (See Figure 13). As with amino acids, proteins improved green strength of the rubber. Gelatin, albumin, and soy proteins improved mechanical properties most effectively, while gluten, gliadin, and zein demonstrated more prominent plasticizing effects.[91] These studies were
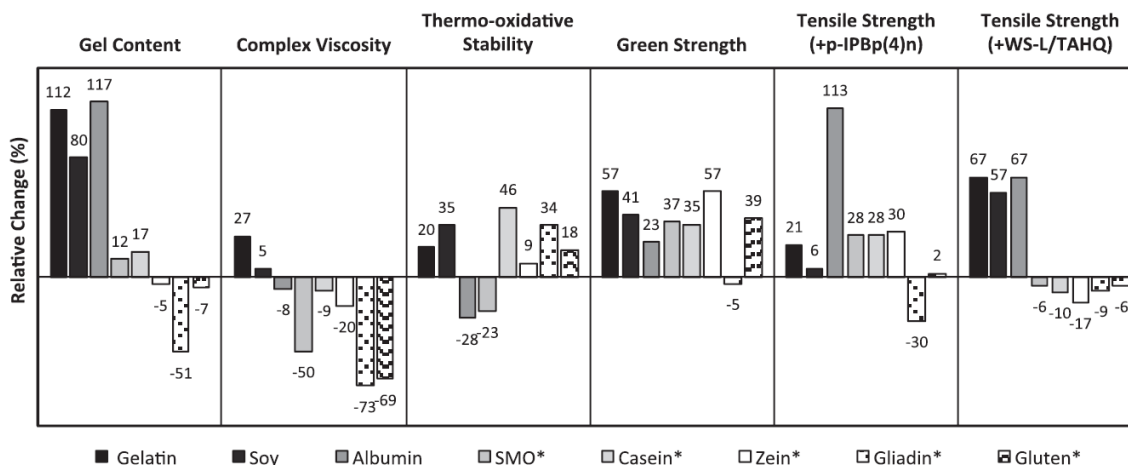
Figure 13: Summary of USDA protein addition to guayule rubber. Rubber improved thermo-oxidative stability in almost all cases.[91]

conducted specifically to alter guayule to perform similarly to hevea rubber, but produced results that can be applied outside of this specific application. Both of these cases indicate that vulcanization and mechanical properties are influenced by different proteins and amino acids, which could be investigated further for use in tire rubber compounds as replacements to 6PPD.

While the use of guayule natural rubber to replace hevea natural rubber is a relatively new area of research, the use of natural antioxidants in natural rubber has been ongoing. Studies into the use of alternative antioxidants in natural rubber compounds have demonstrated the viability of a multitude of different naturally derived antioxidants in replacing currently favored synthetic antioxidants. These studies often involve replacing a synthetic antioxidant with a natural one and studying the performance and characteristics of the result in comparison with the original formula. Often they do not involve significantly altering the rubber formulation. One such study involved comparison of amino acids with 6PPD as rubber antioxidants in radiation vulcanized natural rubber latex. The study indicated that alanine is particularly effective as an antioxidant in natural rubber latex but that the performance of the amino acids as antiozonants was not quite as effective as 6PPD.[92] Komethi et. al. investigated the use of a natural antioxidant derived from oil palm leaves in natural rubber vulcanizates and concluded that its effect on retention of tensile properties after aging was equivalent to that of commercial antioxidants trimethyl quinoline (TMQ) and butylated hydroxy toluene (BHT), thus showing promise as a possible aging retardant for natural rubber.[93] In a similar study, chitosan derivatives were investigated as antioxidants for natural rubber and their effects compared to those of the synthetic antioxidants IPPD and PBN. The findings of this study indicated that the chiotsan-derived antioxidants not only enhanced the properties of natural rubbers but also resulted in retention of tensile and elastic properties of natural rubber after aging compared to the synthetic compounds studied.[94] The experimental use of henna as a natural rubber antioxidant also resulted in retention of tensile properties equivalent to that seen when using TMQ in the same rubber compounds, indicating that henna could also serves as an alternative to some commonly used

synthetic antioxidants.[95] While these studies investigated different types of natural rubbers from various industries with many different naturally derived antioxidants, their promising results indicate that the use of natural antioxidants is a promising area to further explore within the tire industry as it searches for a 6PPD alternative.

7.3   Health and environmental implications of alternative vulcanization schemes

Tire manufacturing as a component that is parallel to rubber processing and manufacturing, includes various concerning occupational exposures. Some concerns within the tire manufacturing industry are various chemical exposures that manifest as particulate matter, fumes and chemical byproducts– of which are regularly monitored for in terms of occupational exposures. Previous studies have shown that excess deaths have been a result of various types of cancer- like bladder, stomach, lung, hematopoietic and other cancers.[96] Permissive exposure limits have not been established for most of the chemicals found in these processes, but all of these occupational exposure should be taken into consideration when surveying potential alternatives to 6PPD.

In terms of changing the vulcanization process such that the temperatures can be lowered from the current standard, making the manufacturing environment less hazardous– specifically regarding burns.Lower temperature processes protect workers from vaporization of chemicals used in the process of rubber vulcanization. However, other issues can arise when changing this scheme, such as the uncertainty behind the products of these low-temperature processes.

When considering ergonomic exposures there are still many unknown factors in changes to processes and machinery used for manufacturing; we assume that the ergonomic circumstances are likely not to change depending on the molecular weight of particles used in the new vulcanization process. Repetitive motion for lifting and human factors may still be of concern for upper and lower lumbar strain and injury, if key ergonomic exposure assessments are not incorporation in the changes to manufacturing processes.

Issues with tire safety may also arise when exchanging a well-studied process with a lesser-known and lesser-studied one. Due to the safety regulations that the tire industry needs to meet, such changes cannot be made lightly and must be evaluated and tested to assess any changes in tire performance and durability.

8 Recommendations and Conclusions

8.1 6PPD Alternatives Comparison

The typical tire formulation incorporates 6PPD in almost every aspect of the tire. Consequently, replacing 6PPD remains a difficult and complex problem. Of the four alternative schemes discussed in this report, no single solution can be deemed optimal due to the vast amount of safety and performance testing required following tire reformulation. However, among the four options we have considered herein, modification of 6PPD will likely result in the easiest industry replacement option. The optimization of tire formulations around the use of 6PPD makes "drop in" replacements attractive, as these replacements are unlikely to require a drastic change in the tire manufacturing process. However, since many of the mechanisms of 6PPD's superior performance as an antioxidant and antiozonant are not fully understood, the modification of the molecule may result in unexpected performance changes. Since the mechanism of toxicity of 6PPDQ to salmon is still under investigation, it is difficult to predict the toxicity of alternatives. Of all of the alternatives, modification of the 6PPD compound is most likely to result in similar toxicity, even if the formation of 6PPDQ can be prevented. Additionally, even if the modified molecule performs well as a drop in solution, extensive toxicity testing is necessary to ensure that this does not result in a regrettable substitution.

The potential for drop in solutions to completely fulfill the role of 6PPD in tire compounds is unknown, and even molecules similar to 6PPD will potentially still require adjustments in current tire formulations. As a result, the complete reformulation of tires may result in the most effective long-term solution for replacing 6PPD, while also ensuring tire performance meets current standards. Of the three remaining solutions, gallates are most like 6PPD with regard to its protective mechanisms, because these compounds can be modified to diffuse through the tire compound at similar or even preferable rates as 6PPD. Aquatic toxicity of gallates remains another issue with the suggested alternatives. Although Coho salmon are the species of interest with regard to 6PPD, replacements should not result in toxicity to other aquatic species, particularly since tire wear particles will continue to enter aquatic environments.

Unlike these small molecules, lignin is a large polymer that will not diffuse through tires at appreciable rates. Still, ignin is a well studied rubber filler compound and could potentially be incorporated into the rubber matrix so that it does not have to diffuse through the tire like 6PPD and other additives, but rather serves as an antioxidant that remains a part of the tire rubber compound. Additionally, studies referenced herein indicate that lignin has positive effects on tire rubber strength performance. Lignin is a relatively diverse and abundant polymer serving as a key structural component of most plants, so its toxicity is less concerning in some respects. However, on an industrial scale, the production of lignin from its constituent monomers presents the most likely toxicity issue with using this alternative. Furthermore, additional changes to the tire formulation to optimize the use of lignin may introduce new threats to human and environmental endpoints of interest.

Finally, reformulation of the tire using alternatives to hevea natural rubber, as well as modification of the vulcanization process, remain the most ambitious and costly solutions. Since vulcanization is essential to almost all rubber applications, changes in this process will

require drastic industry overhaul of rubber processing techniques. However, the reduction in vulcanization temperatures opens up many doors for naturally derived antioxidants to be tested in rubber formulations. In a similar respect, overhauling the rubber formulation of tires using new natural rubbers will require extensive change, but is a promising solution. There is already interest in using domestic sources of natural rubber and changes in current tire formulations are required to make these sources viable alternatives to hevea rubber. This presents a unique opportunity to test new, environmentally friendly antioxidants and antiozonants from the beginning of the formulation process. Much like the tires were formulated to optimize the use of 6PPD, guayule and taraxagum tires could be formulated to optimize use of other antioxidants. Similarly to lignin, predicting toxicity continues to be a challenge if there are drastic changes in tire formulations when replacing hevea rubber.

Even if no replacement can meet the same performance standards of 6PPD, combinations of antioxidants and antiozonants could result in similar protection. These combinations, like all of the solutions discussed, will need to undergo extensive testing. Until these tests are conducted, there is no way to accurately compare the performance of any 6PPD alternatives. The only way to approach the issue of eliminating 6PPD is through dedicated and repetitive reformulation and tire performance analyses.

8.2   Next Steps

As already discussed, the use of 6PPD replacements requires extensive change within the tire industry. The following steps detail the process by which 6PPD alternatives will need to be identified and tested:

1) Identification of 6PPD alternative candidates, as discussed in this report.

2) Performance and toxicity testing of candidates.

3) Rubber compounding tests to ensure viability of alternatives in industrial manufacturing processes.

4) Identification of suppliers of the tested alternative.

5) Wheel and road tests of the tires to ensure performance and safety standards are met.

The solutions discussed in this report are not infallible solutions to the extensive concerns regarding 6PPD; the suggested solutions are rather areas for further research. To prove anything as a viable alternative, not only will all tire performance and safety tests need to be completed, but a thorough hazard assessment would also be required. This issue remains a complex and challenging one, and will require extensive research and trials. Nevertheless, a solution must be aggressively pursued to ensure the survival of the Coho salmon species.

A   Comprehensive hazard table

On the following page we present a hazard table containing the human and environmental hazard data for chemicals associated with gallates and lignin as replacements for 6PPD. Hazards associated with modified versions of 6PPD and with alternative vulcanization and rubber formulation schemes are omitted as these do not represent drop-in replacements for 6PPD and so evade straightforward comparisons. See the main text (Sections 4.2, 7.3, and 8.1) for more details about the predicted environmental hazards accompanying these latter strategies.

Common Trade Name	Group I Human Endpoints					Group II and Group II* Endpoints							Ecotoxicity	Fate		Physical Hazard	
	Carcinogenicity	Mutagenicity	Reproductive Toxicity	Developmental Toxicity	Endocrine Activity	Acute mammalian toxicity	Systemic toxicity	Neurotoxicity	Skin sensitization	Respiratory sensitization	Skin irritation	Eye irritation	Aquatic Toxicity Acute/chronic	Persistence	Bioaccumulation	Reactivity	Flammability
Parent Compound																	
6PPD	DG	DG	DG	H-M	DG	M	DG	DG	H	DG	M	M	vH	L	vH	DG	DG
6PPD quinone	DG	DG	DG	DG	DG	DG	DG	DG	DG	DG	DG	DG	vH	DG	DG	DG	DG
Strategy: Food additives/preservatives																	
Propyl gallate	L	L	L	L	M	M	DG	DG	H	DG	M	H	vH	L	vL	L	L
Octyl Gallate	L	L	L	DG	M	M	DG	DG	H-M	DG	M	DG	H	L	L	L	L
Lauryl gallate	DG	DG	DG	DG	L	L	M	DG	H-M	DG	M	H	H	H	L	L	L
Epigallocatechin gallate	DG	L	M	DG	DG	M	DG	DG	H	DG	M	H	H	vH	L	L	L
Gallic acid	L	L	L	DG	DG	L	L	DG	M	DG	H	H	L	L	vL	L	L
Strategy: Lignin																	
p-Coumaryl alcohol	DG	DG	DG	DG	DG	DG	M	DG	H	DG	H	H	DG	DG	L	L	L
coniferyl alcohol	DG	DG	DG	DG	DG	DG	M	DG	H	DG	H	H	DG	DG	DG	L	L
Sinapyl alcohol	DG	DG	DG	DG	DG	DG	M	DG	H	DG	H	H	DG	DG	DG	L	L
Lignin	L	L	L	L	L	L	L	L	L	L	L	L	L	L	L	L	L

Figure 14: Comparative human and environmental hazard data for all chemicals associated across strategies presented in this document relative to those of 6PPD and 6PPDQ

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