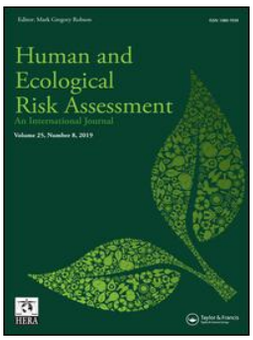

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Human health risk assessment of Tire and Road Wear Particles (TRWP) in air

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ABSTRACT

This risk assessment addresses potential human health impact of exposure to tire and road wear particles (TRWP), which are formed at the interface of the pavement and road comprising rubber with embedded mineral from the pavement. To conduct the risk assessment, we reviewed literature on hazards associated with and exposures to TRWP and developed a screening value for TRWP reliant on the available hazard data and appropriate dosimetric adjustments. The species- and time- adjusted no-observed-adverse-effect-concentration (NOAEC) for respirable TRWP was 55 μg/m3. This NOAEC was compared to exposure estimates for respirable TRWP for both typical and worst case exposure scenarios based on age-specific activity patterns to determine the margin of exposure for TRWP. The estimated daily exposure to TRWP ranged from 0.079 to 0.147 μg/m3, resulting in a margin of exposure for TRWP ranging from approximately 400 to 700. Though there remain uncertainties in the risk assessment stemming from both the hazard and exposure assessments, the current weight of evidence suggests that TRWP presents a low risk to human health.

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Introduction

For over 20 years, exposure to ambient particulate matter (PM) has been a recognized health hazard, particularly as it relates to cardiopulmonary outcomes (Dockery et al. 1992; Peters et al. 2001; Chen et al. 2004; Lin et al. 2005; Pope et al. 2006; Pope et al. 2008). More recently, additional health outcomes have been proposed to be associated with ambient PM, including developmental, reproductive and cancer outcomes (World Health Organization (WHO) 2005; IARC 2016; Wu et al. 2016). Among the various sources of ambient PM, non-exhaust vehicular emissions, such as brake and tire wear, have historically contributed a relatively small proportion to ambient PM, though these particles are less-well studied than exhaust emissions. However, recent regulatory management polices addressing stationary sources, vehicular exhaust and other sources of ambient PM have resulted in an increasing importance on the study of non-exhaust

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vehicular emissions, which include brake wear, tire wear, pavement wear, and resuspended road dust (Amato et al. 2011; Sundvor et al. 2012; Amato 2018).

The focus of this risk assessment is on human inhalation exposures to tire and road wear particles (TRWP), one of the contributors to non-exhaust vehicular particulate emissions. TRWP are formed during abrasive processes at the interface of the tire and roadway surface. These particles include polymeric rubber originating from the tire, along with embedded mineral from the pavement and have been characterized with respect to chemistry, size, and morphology (Kreider et al. 2010). The size distribution of TRWP indicates that they are primarily found in the non-respirable size range, with a unimodal distribution centered at approximately 75 um. The general composition of TRWP includes plasticizers and oils (10%), polymers (16%), carbon black (13%), and minerals (61%), based on thermogravimetric analysis. Silicon, zinc, aluminum, calcium, iron, and magnesium are the predominant metals present in TRWP and total PAHs are found at 12.71 ppm. Though the size distribution of TRWP indicates that these particles are predominantly found in the non-respirable size range, some TRWP can be found in the airborne fraction (Dannis 1974; Gustafsson et al. 2008; Kreider et al. 2010; Panko et al. 2013; Panko et al. 2019). Some researchers have proposed that TRWP may contribute to nanoparticle exposures, though it is unclear if the particles generated from abrasion during driving are TRWP (Dahl et al. 2006; Sjodin et al. 2010; Mathissen et al. 2011). Emissions estimates for airborne particles originating from tires in the PM_{10} fraction range from 2.4 to 13 mg/vkm, with an average of 6.3 mg/vkm (Panko et al. 2018), based on emissions inventory estimates, receptor modeling, road simulation studies, and empirical roadside monitoring data.

Though research on tire wear exposure and hazard has been conducted over the past two decades, as yet, a comprehensive and quantitative risk assessment for TRWP is lacking. The purpose of this work is to evaluate the available literature to understand the potential for human health risk, with a focus on cardiopulmonary outcomes, associated with exposure to TRWP from ambient air. Oral and dermal exposure to TRWP is expected to be *de minimis* compared to inhalation exposure, and thus is not considered within this review. To achieve the goal, we reviewed literature relevant to addressing toxicity and exposure associated with particulate matter originating from tires to identify the most appropriate studies on which to base a risk assessment for TRWP. Based on that review, we aimed to predict the margin of exposure (MOE) for TRWP for relevant exposure scenarios, including sensitive and highly exposed sub-populations.

Risk assessment framework

To complete the risk assessment for human exposure to TRWP in air, the guidelines published by the National Academy of Sciences and U.S. EPA were followed (National Academy of Sciences 1983; U.S. EPA 1989; U.S. EPA 2002). These guidelines recommend that risk assessments should contain some or all of the following four steps: hazard assessment, dose-response assessment, exposure assessment, and risk characterization.

Hazard assessment

Within the framework of classic risk assessment, the purpose of hazard assessment is to identify the adverse health effects that may occur with exposure to the substances of

interest in the risk assessment. In this case, the interest is TRWP, which is a complex mixture of tread rubber and embedded pavement from the road. In order to evaluate potential human health hazards associated with TRWP, literature addressing effects occurring with mammalian exposure to TRWP was identified and reviewed. Using the Toxicology filter, PubMed was searched to identify potentially relevant articles using the following search terms: tire OR tyre. This search resulted in 715 results, of which all were reviewed for relevance. In addition, a supplemental literature search was conducted in Google Scholar using the search terms: (tire or tyre) AND toxicity, with the first 200 of 939 results, ranked by relevance to the search terms, reviewed in full to identify appropriate literature. Results of the literature searches were screened to identify the most appropriate papers. Papers were excluded for further consideration if they 1) focused only on ecological toxicity; 2) did not address tire wear (e.g. focused on particles associated with other portions of the tire life cycle, i.e. waste management); 3) addressed only ambient air particulate without considering specific effects associated with tires; 4) did not address the inhalation pathway as the relevant route of exposure 5) addressed only the toxicology of street dust or general ambient particulate matter 6) were review papers only and 7) were not published in English. All papers remaining following the screening were reviewed in full and relevant information gathered. Additionally, we reviewed any relevant articles within the reference lists of the identified papers. Studies deemed most relevant for risk assessment included those addressing *in vivo* responses, with a focus on those evaluating TRWP, including both rubber and mineral incrustation.

Few studies were identified that addressed potential hazards associated tires and their wear products. In *in vitro* models using extracts of tire tread or tread particles (TP), researchers have reported cytotoxicity, genotoxicity and oxidative stress in A549 cells (Gualtieri et al. 2005; Beretta et al. 2007; Gualtieri et al. 2008), genotoxicity and inflammatory response in macrophage and lung epithelial cell lines (Karlsson et al. 2006; Lindbom et al. 2006; Lindbom et al. 2007; Karlsson et al. 2011; Poma et al. 2019). Others have noted potential aryl hydrocarbon receptor activity, as well as endocrine activity of extracts from tires (Zhang et al. 2002; He et al. 2011). Studies in animal models, however, are equivocal, with some authors reporting cytotoxicity and inflammation (Mantecca et al. 2009; Mantecca et al. 2010) and others reporting small transient effects on inflammation in the absence of cytotoxicity (Gottipolu et al. 2008) following instillation of TP. Of these studies, none evaluate effects of TRWP as a composite mixture. Given that these particles are known to be both chemically and morphologically distinct from TP, effects observed in these studies may over or under predict hazards associated with TRWP (Kreider et al. 2010). Furthermore, organic extracts of tread rubber may not accurately represent what is extracted in the lung following inhalation. Lastly, Gerlofs-Nijland (Gerlofs-Nijland et al., 2019) evaluated the effect of non-exhaust emissions, including studded tire and pavement wear, in the PM2.5 fraction in mice. However, because of the presence of studs in the tires, the characteristics of particles generated may deviate from TRWP; without characterization of these particles, their identity cannot be confirmed

One study was identified that evaluated human health hazards associated with TRWP (i.e. particles that contained both tread rubber and embedded pavement). Furthermore,

this was the only *in vivo* study identified that utilized an inhalation exposure regimen, as compared to instillation. Kreider, et al. (2012) conducted a 28-day inhalation study with TRWP in male and female rats following Organisation for Economic Co-operation and Development (OECD) Test Guideline 412 (OECD 2018). Rats were exposed to aerosolized respirable (10 µm and smaller) TRWP for 6 h per day over 28 days. Target exposure concentrations were 0, 10, 40, and 100 µg/m^3. Table 1 describes the characteristics of the particulate in each of the TRWP exposure groups based on measured data.

Following this exposure regimen, all animals were sacrificed and evaluated for evidence of cardiopulmonary effects, including pulmonary inflammation, cytotoxicity in respiratory tract, evidence of oxidative stress, lung histopathology, abnormal clinical chemistry, and altered clotting factors. There were no adverse effects of TRWP detected at any concentration for any marker. Based on these results, a No-Observable-Adverse-Effect-Concentration (NOAEC) of 112 µg/m3 was identified for TRWP (Kreider et al. 2012).

Dose response assessment

The purpose of the dose response assessment portion of a risk assessment is to characterize the relationship between the dose of a substance and the likelihood of an adverse health effect in the exposed population (National Academy of Sciences 1983). Within the context of the dose response assessment, one must consider factors such as sex, species, susceptible populations, and sources of uncertainty in the toxicity assessment. The basic steps of dose response assessment for non-carcinogenic health effects include:

- Identification of the critical effect level (e.g. No-Observable Adverse Effect Level [NOAEL] or NOAEC),
- Adjustment of NOAEL or NOAEC based on dosing regimen, and
- Adjustment of NOAEL or NOAEC to human equivalent concentration, if in animal study

Following these steps, the resulting screening value can be compared to an average daily exposure concentration based on measured data to determine the margin of exposure between actual exposure levels and the level at which harm may occur.

Identification of critical effect level

In evaluating the available hazard data for TRWP, many of the studies relied on methods that are difficult to translate in a dose response assessment. *In vitro* studies are

Table 1. Measured characteristics of aerosolized TRWP by treatment group.

Target concentration (µg/m3)	Measured concentration (SD) (µg/m3)	NMAD (GSD) (um)	MMAD (GSD) (µm)	% Mass < 3 um
100	112.2 (29.7)	1.29 (1.60)	3.68 (1.83)	45.7
40	37.8 (19.1)	1.13 (1.56)	3.04 (1.80)	56.6
10	12.5 (10.5)	1.04 (1.46)	2.38 (1.81)	71.0

SD = Standard deviation; NMAD = Number median aerodynamic diameter; MMAD = Mass median aerodynamic diameter; GSD = Geometric standard deviation.

useful for hazard screening and often can be used to investigate the mechanism of action by which a toxicant operates. Similarly, intratracheal instillation studies are useful for hazard assessment and relative potency evaluation, but it is often difficult to extrapolate doses utilized in these studies, along with *in vitro* studies, to relevant NOAELs or NOAECs on which to base a dose response assessment. Therefore, considering these factors and the available literature on tire-related particle hazards, Kreider, et al. (2012) was identified as the most appropriate study from which to develop a screening value for TRWP. This study was selected primarily because it evaluates effects of TRWP in an *in vivo* mammalian model that can easily be accommodated in a dose response assessment using the test substance that was most representative of the complex tire tread and pavement containing particles present in ambient air. Additionally, the study was performed in accordance with OECD TG 412 for 28-day (subacute) inhalation toxicity studies, which are intended to be used to "identify and assess human residential, consumer, transportation, and environmental risk." The NOAEC for TRWP was 112 μg/m^3. This was the highest concentration tested in the critical study, and therefore the true no-effect level may be higher. However, because the data are not amenable to benchmark dose modeling (extrapolation to identify the NOAEC), this value was selected for determination of the critical effect level for TRWP.

Adjustment of NOAEC based on dosing regimen

In order to appropriately compare the critical effect level to an exposure concentration to which humans may be exposed, the critical effect level must take into consideration the pattern of exposure, both in the exposed population and in the design of the original study. In the study in which the NOAEC was identified, rats were exposed for 6 h per day for 7 days per week. Equation 1 is used to adjust the NOAEC from the animal study into a time-adjusted NOAEC ($NOAEC_{Adj}$), based on the exposure pattern of the exposed population.

$$Equation\ 1:\ NOAEC_{Adj} = NOAEC \times \frac{ED_{as}}{ED_{es}} \times \frac{EF_{as}}{EF_{es}},\ such\ that$$

ED_{as} = Exposure duration for animal study (hrs)
ED_{es} = Exposure duration for human exposure scenario (hrs)
EF_{as} = Exposure frequency for animal study (days)
EF_{es} = Exposure frequency for exposure scenario (days)

The general population has the potential to have continuous exposure, 24 h per day, 7 days per week. Based on this scenario and the dosing regimen of the inhalation study, the $NOAEC_{Adj}$ is 28 μg/m^3.

Adjustment of NOAEC based on species differences

Because the respiratory tract structure of animal models differs from the respiratory tract of humans, the dose of inhaled particles delivered to the human lung may differ from that delivered to the rat lung given the same external concentration of particulate. In order to scale an exposure concentration (external concentration) for particulate to determine a screening value applicable to humans, this difference needs to be

considered. The U.S. EPA has developed a model for particulate matter to determine the regional deposited dose ratio (RDDR) between humans and a variety of animal models, including rat, mouse, and hamster, as part of their guidance for determining reference concentrations (RfCs) (U.S. EPA 2002). Using this model, one can input particulate characteristics, such as mass median aerodynamic diameter (MMAD) and geometric standard deviation of the MMAD to determine the RDDR. The RDDR is then used, according to Equation 2, to determine the human equivalent NOAEC ($NOAEC_{HEC}$).

$$Equation\ 2:\ NOAEC_{HEC} = NOAEC_{Adj} \times RDDR$$

The U.S. EPA RDDR program was used to predict the appropriate RDDR for the Kreider, et al. (2012) study, relying on particle characteristics outlined in Table 1. Average body weights from the final day of study for the highest dose group (309 g) were also used as inputs in the model. This program calculates RDDRs for different regions of the lung, and an appropriate RDDR should be selected based on the region of the lung in which an effect was identified. Because no effect was identified in any part of the respiratory tract in Kreider, et al. (2012), the RDDR for the entire respiratory tract was used for calculation of the human equivalent NOAEC in this risk assessment. Table 2 summarizes the results of this adjustment.

Exposure assessment

Exposure assessment is the process through which the exposure of biological receptors (humans in the case of health risk assessment) to substances present in the environment is estimated and/or measured. Components of an exposure assessment include estimates of exposures based magnitude and duration of exposure and identification of exposure scenarios based on exposed population and exposure patterns. Collectively, these two components are used to determine scenario-specific exposure estimates that can be used for comparison to screening values to determine the risk for that scenario.

Review of TRWP exposure studies

To identify appropriate exposure assessment information for TRWP, an approach similar to that outlined for hazard data was followed. First, PubMed was searched to identify potentially relevant articles using the following search terms: tire OR tyre AND (air OR source apportionment). This search resulted in 264 results. In addition, a supplemental literature search was conducted in Google Scholar using the search terms: (tire or tyre) AND wear AND air AND (exposure or risk), with the first 500 of 18,300 results, ranked by relevance to the search terms, reviewed in full to identify appropriate literature. Results of the literature searches were screened to identify the most appropriate papers. Papers were excluded for further consideration if they 1) addressed non-

Table 2. Key information on calculation of $NOAEC_{HEC}$ for TRWP.

NOAEC ($\mu g/m^3$)	$NOAEC_{Adj}$ ($\mu g/m^3$)	RDDR	$NOAEC_{HEC}$ ($\mu g/m^3$)
112	28	1.955	55

airborne exposures (e.g. soil, sediment, water, road dust, etc.); 2) focused on exposures from other life cycle stages of tires (e.g. end-of-life, manufacturing); 3) focused on particulate generation from tires in a laboratory environment; 4) focused on health outcomes associated with ambient air pollution (e.g. epidemiology studies); 5) were toxicology studies on particulate; 6) addressed functional properties of tires (e.g. inflation, rolling resistance, etc.); 7) addressed occupational exposures; 8) provided only information on general ambient particulate matter concentrations and 9) were not published in English. Given the complexity of this topic, we evaluated review papers to identify other candidate papers for consideration, unlike with the hazard literature. All papers remaining following the screening were reviewed in full and relevant information gathered. Additionally, we reviewed any relevant articles within the reference lists of the identified papers. Studies deemed most relevant for risk assessment included those reporting empirical measurements of TRWP in air. Studies reporting on emission factors from tires in the absence of empirical measurements of TRWP were considered qualitatively; however, precedent was given to studies with measured data, in lieu of relying on modeled estimates of TRWP contribution.

Several researchers have attempted to estimate the contribution of tires to particulate in the environment using a variety of proposed markers for tires, including metals (primarily zinc), tire chemicals, and rubber polymers (Cardina 1974; Pierson and Brachaczek 1974; Cadle and WIlliams 1979; Cadle and WIlliams 1978; Cadle and WIlliams 1980; Spies et al. 1987; Kim et al. 1990; Rogge et al. 1993; Yamaguchi et al. 1995; Kumata et al. 1997; Rauterberg-Wulff 1998; Fauser 1999; Kumata et al. 2002; Schauer et al. 2002; Almeida-Silva et al. 2011; Kumata et al. 2011; Schmid 2000). In spite of these efforts, however, few authors report reliable estimates of TRWP in the air. Of the markers used in these studies, many lack specificity for tires, have not been fully developed or validated, and are therefore of questionable utility for accurately characterizing TRWP concentrations in the environment. Furthermore, of the sampling for airborne TRWP, many researchers focused on areas of probable high concentrations, such as near or within tunnels, in an effort to increase the likelihood of detection and, in some cases, estimate emission factors for tires. Unice, et al. (2012) has recently reported the development of a pyrolysis-gas chromatography method that relies upon polymer fragments specific to rubber polymers used in passenger tires for use in environmental measurement of TRWP. This marker was utilized in a global sampling effort conducted by Panko, et al. (2013).

Panko, et al. (2013) aimed to evaluate TRWP concentrations in locations representative of potential human exposure. Sampling locations of geographically diverse locations were selected in France, the United States, and Japan. Sampling locations were also paired with a sediment sampling program, where samples were collected using a watershed approach. Thus, the air samples were collected in cities and towns throughout the watershed. Specific site selection criteria included the presence of an identifiable vehicle traffic source and a diversity of residential, commercial, school, urban, rural and recreational settings. All air samples were collected near the roadside with distance from the road differing based on logistical considerations, such as accessibility and availability of electric power for sampling equipment, traffic load, population density, and site security. Air samples were size-selective, aimed at collecting particulate 10 μm in size or smaller

Table 3. Summary results from TRWP global air sampling campaign by Panko et al. (2013).

		Air concentration (μg/m^3)		
Country	N	Mean	Maximum	95th UCL of mean
France	27	0.243	1.34	0.565
Japan	27	0.102	0.32	0.123
United States	27	0.135	0.48	0.169
All	*81*	*0.160*	*1.34*	*0.275*

(PM10). In total, 27 PM10 air samples were collected in each country for a total of 81 air samples.

The key results of Panko, et al. (2013), including mean concentration, maximum concentration, and 95th upper confidence limit (UCL) of the mean concentration for TRWP by country and overall are presented in Table 3. Upper confidence limits on the mean were determined using ProUCL (U.S. EPA 2007). Detection frequency, across all samples, was 74%, indicating TRWP is ubiquitous in ambient air. However, relative contributions of TRWP to ambient PM10 were, on average, less than 1%. In addition to the study on TRWP in PM10, Panko, et al. (2019) evaluated TRWP in PM2.5, finding that TRWP is also present at low concentrations (0.030 μg/m3) in the smaller size range, representing a low proportion (<0.3%) of total ambient PM2.5.

Selection of data for exposure point concentrations (EPCs)

Based on the specificity of the marker for TRWP and representativeness of the sampling locations (i.e. targeted at locations for human exposure vs. worst-case exposure scenarios), TRWP measurements in PM10 from Panko, et al. (2013) were identified as the most appropriate for use as exposure point concentrations (EPCs) in this risk assessment. These data represent estimates of TRWP in air using the most representative marker and locations and are comparable to the toxicity data available for TRWP (which is focused on the PM10 fraction). Furthermore, as PM10 measurements are inclusive of PM2.5, this exposure estimate would account for TRWP in both fractions.

Characterizing exposure scenarios

In order to predict risk of adverse health effect associated with exposure to TRWP, it is necessary to identify and appropriately characterize the exposed populations, including typical and high-end exposed populations. In the case of TRWP, because it is found ubiquitously in the ambient air, the general population, including children and adults, are exposed to TRWP on a daily basis. For the purpose of this risk assessment, we estimated exposure concentrations for children and adults in various age groups. These groups represented the typical exposure population. Because TRWP is found in the outdoor ambient environment, outdoor workers may have, on average, higher daily exposures due to their work outdoors where TRWP concentrations are predictably higher. To account for a worst case and typical exposure scenarios, we calculated exposure for the following populations: adult outdoor worker (e.g. road crew, street vendor, parking or valet attendant, policeman, etc.), general population adult, general population retired adult, infant (< 1 year), child (1-16 years), and teenager (16-21 years).

Table 4. Distribution of time (minutes) spent in microenvironments by exposure group.

Age group (yrs)	Outdoor	Transit	Indoor, residential	Indoor, institutional	Total (min)
Infant (<1)	44	43	1353	0	1440
Child (1 - 16)*	132	64	1086	158	1440
Teenager (16 to < 21)	102	90	1090	158	1440
Adult (21–65)	180	101	851	308	1440
Adult Retiree (>65)	211	87	1142	0	1440
Outdoor Worker	488	101	851	0	1440

*Used maximum time for outdoors for all ages in this group to be conservative.

For each of these exposure groups, the pattern of exposure is different for each day, as each group may spend differing amounts of time in various microenvironments (e.g. residential indoor space, outdoors, vehicles, etc.). Table 4 summarizes the exposure patterns used for this risk assessment for each group. Outdoor, transit and total indoor time are adapted from U.S. EPA Exposure Factors Handbook (Chapter 16: Activity Factors). Residential vs. institutional indoor time was differentiated using data from U.S., EU, Korea and Japan and is based on time children spent in school per year and time adults spend at work per year (UNESCO 2010/2011; European Foundation for the Improvement of Living and Working Conditions 2011; U.S. EPA 2011; European Commission 2013; OECD 2013).

Differentiation of time spent in the different microenvironments by exposure group is essential given that the concentration of TRWP in air will differ depending on the microenvironment. Wilson, et al. (2000) evaluated the infiltration of particulate from ambient air into indoor spaces, including indoor residential environments (with open and closed windows), indoor institutional environments, and transit (e.g. automobiles, etc.). These infiltration ratios can be applied to the outdoor TRWP concentrations measured in the sampling campaign to appropriately adjust the exposure based on time spent in different microenvironments. We relied upon the values reported in Wilson, et al. (2000) for infiltration ratios for PM10. Because the infiltration ratios differ for indoor residential spaces with open vs. closed windows, an average value of the two was used to account for both possible scenarios. The infiltration ratios used in calculating daily average exposure concentration of TRWP are found in Table 5.

Calculating daily TRWP concentrations for each exposure scenario

To calculate daily average exposure concentrations for TRWP, the microenvironment and infiltration ratio information were used to adjust the outdoor exposure concentration in accordance with the time spent in each microenvironment. Equation 3 was used to calculate TRWP exposure for each respective microenvironment (indoor, outdoor, transit) and Equation 4 was used to calculate total daily TRWP exposure for each population group.

$$Equation\ 3:\quad E_{microenvironment} = E_{EPC} \times IR_{microenvironment} \times \frac{T_{microenvironment}}{T_{day}}$$

Such that:

E_{EPC} = 95th UCL of mean for all regions from Panko et al. (2013);

$IR_{microenvironment}$ = Infiltration ratio for microenvironment;
$T_{microenvironment}$ = minutes spent in microenvironment; and
T_{day} = total minutes in day (1440)

$$Equation\ 4: \quad E_{total} = E_{indoor} + E_{outdoor} + E_{transit}$$

Such that:

E_{total} = Average daily exposure concentration for TRWP

E_{indoor}, $E_{outdoor}$, and $E_{transit}$ = Average daily exposures to TRWP for the respective microenvironment

Daily exposure calculations by population and microenvironment can be found in Table 6.

Risk characterization

The final step in the risk assessment is risk characterization, which uses information derived from the hazard, dose response, and exposure assessments to inform about the likelihood of a health risk. For TRWP, the screening value is identified as the $NOAEC_{HEC}$ and is compared to the daily exposure concentrations to understand the likelihood of risk. For this risk assessment, we used a margin of exposure (MOE) approach, comparing the NOAEC directly to the exposure concentration without incorporation of uncertainty factors. As recommended by regulatory guidance, we used a statistical representation of a reasonable upper bound for exposure point concentration (EPC), the 95th UCL of the mean, to calculate the MOE. MOE is calculated using Equation 5:

$$Equation\ 5: MOE = \frac{NOAEC_{HEC}}{EPC}$$

MOEs for TRWP range from approximately 400 to 700 for the relevant exposure scenarios (Table 7); the lowest MOE was for outdoor workers, whereas the highest MOE was for infants. The range generally reflected extremes of time spent indoors and outdoors, respectively.

Discussion

Overview of risk assessment

The purpose of this work was to understand the potential for risk from exposure to TRWP in ambient air, based on studies of hazard and exposure to TRWP. In reviewing the literature on hazard and exposure, few studies were identified that specifically

Table 5. Selected infiltration ratios for calculation of average daily TRWP exposure.

Microenvironment	Infiltration ratio
Indoor, residential (average of open and closed windows)	0.25
Indoor, institutional	0.2
Transit	0.7
Outdoors	1.0

Table 6. Daily TRWP exposure concentrations by population group and microenvironment based on 95th UCL of mean measured TRWP concentrations from sampling campaign.

Exposure scenario	Exposure duration (min)	Infiltration factor	95th UCL mean (μg/m^3)	Average daily exposure (μg/m^3)
Infant (<1)				
Indoor, residential	1353	0.25	0.275	0.065
Indoor, institutional	0	0.2	0.275	0.000
Outdoor	44	1	0.275	0.008
Transit	43	0.7	0.275	0.006
TOTAL	1440			**0.079**
Child (1 - 16)*				
Indoor, residential	1086	0.25	0.275	0.052
Indoor, institutional	158	0.2	0.275	0.006
Outdoor	132	1	0.275	0.025
Transit	64	0.7	0.275	0.009
TOTAL	1440			**0.092**
Teenager (16-21)				
Indoor, residential	1090	0.25	0.275	0.052
Indoor, institutional	158	0.2	0.275	0.006
Outdoor	102	1	0.275	0.019
Transit	90	0.7	0.275	0.012
TOTAL	1440			**0.090**
Adult (21-64)				
Indoor, residential	851	0.25	0.275	0.041
Indoor, institutional	308	0.2	0.275	0.012
Outdoor	180	1	0.275	0.034
Transit	101	0.7	0.275	0.014
TOTAL	**1440**			**0.100**
Retired Adult (>64)				
Indoor, residential	851	0.25	0.275	0.055
Indoor, institutional	0	0.2	0.275	0.000
Outdoor	488	1	0.275	0.040
Transit	101	0.7	0.275	0.012
TOTAL	**1440**			**0.106**
Outdoor Worker				
Indoor, residential	851	0.25	0.275	0.041
Indoor, institutional	0	0.2	0.275	0.000
Outdoor	488	1	0.275	0.093
Transit	101	0.7	0.275	0.014
TOTAL	**1440**			**0.147**

Table 7. MOEs by exposure scenario.

Exposure scenario	$NOAEL_{HEC}$ (μg/m^3)	Daily exposure (μg/m^3)	MOE
Infant	54.74	0.079	695
Child	54.74	0.092	597
Teenager	54.74	0.090	611
Adult	54.74	0.100	546
Retired Adult	54.74	0.106	514
Outdoor Worker	54.74	0.147	372

addressed TRWP. In particular, for hazard assessment, though researchers have evaluated particles and/or organic extracts of ground tread, few researchers addressed the composite mixture that occurs when a tire wears along a road surface and incorporates mineral from the pavement into the particulate mixture. Kreider, et al. (2012) represents the most robust study on TRWP for use in a risk assessment, as it utilizes TRWP generated on a road simulator and thus includes embedded pavement, and it was conducted in an *in vivo* system, permitting a prediction of dose response for identification of a screening value for use in risk assessment. Similarly, of the available studies on TRWP

measurements in air, only Panko, et al. (2013) utilizes a marker that has specificity to TRWP and considers exposures in areas representative of human receptors, as opposed to in areas of high concentration of traffic-related particulate (e.g. tunnels). This risk assessment relied on these two studies to predict potential risk to humans, including children and highly-exposed outdoor workers, from inhalation of TRWP in ambient air. The results of this assessment indicated the MOE for TRWP ranged from approximately 400 to 700, depending on the exposed population and the pattern of exposure due to time spent in different microenvironments.

Interpretation of an MOE can vary depending on the chemical, its associated hazard and dose response and, in some instances, the regulatory agency or risk assessor conducting the assessment. For example, for chronic non-cancer health effects, the U.S. EPA, as part of their Sustainable Futures Program, has indicated that an MOE greater than or equal to 100 indicates a low potential for risk, when the MOE is based on a no-observed adverse effect level/concentration (U.S. EPA 2013). If the MOE is based on a lowest-observable adverse effect level/concentration (Lowest-Observable-Adverse-Effect-Level (LOAEL)/C), an MOE of 1000 or greater is needed to draw such a conclusion. For genotoxic carcinogens, the European Food Safety Authority (EFSA) requires an MOE of 10,000 to conclude a low likelihood of health risk (EFSA 2012). Other factors which may influence professional judgment regarding an acceptable MOE include: duration of toxicity study (e.g. subchronic vs. chronic) providing the basis for the NOAEL/C, uncertainties in the quality of the data (exposure or hazard), the probability of underestimated exposure, and concerns for sensitive subpopulations. Therefore, in drawing conclusions regarding the likelihood of human health risk from TRWP, we considered many of these factors when evaluating uncertainties and limitations in this risk assessment.

Uncertainties and limitations

In order to draw conclusions regarding the MOEs predicted for TRWP from this analysis, a complete understanding of uncertainties and limitations in the analysis as well as their impact on the potential for human health risk are essential.

Uncertainties in the hazard assessment

Kreider, et al. (2012) provided the basis for the hazard and dose response assessment used in this risk assessment. In this study, animals were exposed to TRWP for 28 days and evaluated for potential impacts on cardiopulmonary outcomes. Based on the results of this study, a NOAEC of 112 µg/m3 was identified, representing the highest concentration of TRWP tested. Therefore, the true threshold for a response is likely to be higher, but uncertain. We expect the true threshold for cardiopulmonary toxicity for TRWP to be higher than 112 µg/m3, based on the observed relative potency to diesel exhaust particles. In a companion instillation study to Kreider, et al. (2012), diesel exhaust particles were a more potent cardiopulmonary toxicant than TRWP in eliciting inflammatory, cytotoxic, and oxidative stress responses in the rat lung. In short-term repeat dose inhalation studies, diesel exhaust particles do not typically elicit effects on

these endpoints at exposure levels below 230 µg/m3 (Sato et al. 2001; McDonald et al. 2004; Banerjee et al. 2009; Gottipolu et al. 2009; Gerlofs-Nijland et al. 2010). Given that TRWP is expected to be less potent than diesel exhaust particles based on the instillation studies, the true NOAEC for TRWP could be at least two-fold higher. Furthermore, the U.S. EPA defined reference concentration (RfC) for diesel exhaust, intended to be protective of even chronic exposures to diesel exhaust particles, is 5 µg/m^3, which is 20-fold higher than the typical concentrations of TRWP found in the ambient air. This comparison suggests that TRWP is unlikely to be a risk to human health, particularly as evidence suggests TRWP is less potent at initiating effects than diesel exhaust.

Additionally, Masano, (1988) conducted a chronic inhalation study of tread particles from studded tires. In this study, they exposed animals to doses of 100, 300, and 1000 µg/m3 of tread particles for 18 h per day, 5 days per week, for 1.5 years and found no adverse effects at 100 or 300 µg/m^3 (Masano 1988). Although the studded tire tread particles are not equivalent to TRWP, the results of this study also suggest that the NOAEC for TRWP may be underestimated, given that the NOAEC for tread particles is 300 µg/m3. If the true NOAEC were higher than that which is used in this risk assessment, the MOE would be commensurately higher.

In addition to uncertainties around the threshold for adverse effect for TRWP, additional uncertainties exist in hazards associated with TRWP based on the study design and intent. Firstly, the particles studied in Kreider, et al. (2012), though representing TRWP in the PM10 fraction, may not fully represent the entire distribution of particles generated during abrasion, including the potential for smaller particles than the animals were subject to in Kreider, et al. (2012). Secondly, the study design by Kreider, et al. (2012) utilized a 28-day (e.g. less-than-chronic) exposure paradigm. Though effects were not observed, there is potential for adverse effects to emerge with longer exposure regimens. However, with the range of MOEs found from this risk assessment, it is not anticipated that even a chronic exposure to TRWP would result in adverse cardiopulmonary outcomes; typically a 10-fold uncertainty factor is sufficient to account for extrapolation from a less-than-chronic exposure regimen.

Thirdly, the risk assessment presented here focuses on what many, including the WHO , believe to be the most common and important outcomes associated with exposure to particulate matter, cardiopulmonary outcomes, often associated with short-term exposures and/or fluctuations in particulate matter (WHO 2005). However, because of the study design (e.g. study duration), endpoints evaluated, and intent of the risk assessment, other adverse effects potentially associated with exposure to TRWP cannot be definitively excluded. For example, ambient particulate matter has been proposed as a carcinogen and reproductive hazard (IARC 2016; Wu et al. 2016). Though TRWP has not been explicitly studied for these endpoints and the potential for TRWP to cause such effects at sufficient exposure level and/or after longer durations of exposure cannot be eliminated, current data suggests that TRWP is unlikely to contribute significantly to the effect of ambient air pollution on these endpoints. First, based on studies conducted by Panko, et al. (2013, 2019), TRWP contributes only a very small amount to ambient PM in developed countries, both in the PM10 and PM2.5 fractions. Secondly, the annual ambient air quality guideline established for PM10 by the WHO representing

the lowest levels at which adverse effects (including cardiopulmonary and cancer) have been observed with 95% confidence is 20 μg/m^3, far above the concentrations of TRWP found in ambient air. Therefore, though current studies cannot completely eliminate the possibility that TRWP could cause effects outside of the respiratory tract, the likelihood that these effects would occur at the concentrations of TRWP found in the environment is very low.

Lastly, the TRWP evaluated in Kreider, et al. (2012) were generated using a laboratory-based machine, and though intended to best replicate driving conditions occurring on the road, may vary from some TRWP generated on-road in terms of characteristics such as polymer content, particle morphology, and particle size distribution. This risk assessment relies on the assumption that TRWP generated in the laboratory are representative of those generated in the environment. Though variations in the particles are possible depending on specific driving conditions, road surfaces, and tire types, it is unknown how much these variations may affect TRWP toxicity. That said, these particles represent the currently best available resource for studying true TRWP.

Uncertainties in the exposure assessment

In addition to uncertainties related to the hazard assessment, there remain a few uncertainties as it relates to the exposure assessment, including: representativeness of the exposure estimate to other environments; assumptions regarding the exposure scenarios (time spent in microenvironments, time with open vs. closed windows); and assumptions about the marker that underlie the estimated TRWP concentrations reported in Panko, et al. (2013). Collectively, these uncertainties could represent over- or underestimates of risk.

In Panko, et al. (2013), sampling occurred in developed countries with programs to manage ambient particulate matter, infrastructure systems to maintain roads, and strict performance and safety requirements for tires on the market. However, currently no data on TRWP concentrations in air exist for developing countries where these aspects may be less well-managed and TRWP concentrations in ambient air may differ. Other assumptions for the exposure assessment may also differ in developing countries, such as infiltration ratios for buildings or time spent in different microenvironments. Therefore, the exposure assessment for TRWP may not be representative of all regions of the world.

Similarly, the exposure scenarios may deviate from those assumed in this exposure assessment. For the indoor microenvironment, we assumed windows were open 50% of the time; however, in warmer regions where air conditioning is uncommon, windows may be more frequently open. Similarly, in colder regions, windows may be open less frequently than 50% of the time. Therefore, this assumption may under or over predict risk depending on the specific location and conditions. Similarly, deviations from assumptions regarding time spent in different microenvironments could increase or decrease exposure and/or risk, depending on the specific scenarios. We relied on regional data from the U.S. EPA for estimates of transit, outdoor and total indoor time for each exposure scenario, differentiating indoor time between institutional and residential based on data from the U.S., Japan, EU, and Korea. Deviations from these

assumptions could affect overall estimates of exposure. As an example, our high-end exposure estimate was for an outdoor worker, who is estimated to spend 488 min outdoors daily. However, there may be examples of individuals who spend far more time than the outdoor worker in the outdoor environment (e.g. homeless individuals). At this time and without being able to predict all possible exposure scenarios with specificity, we believe the assumptions used in this risk assessment are reasonable approximations of the most common exposure scenarios.

Regarding the exposed populations, this risk assessment, though accounting for different age ranges, does not specifically address sensitive subpopulations, such as children (who may have increased sensitivity to adverse effects associated with particulate matter) or adults engaging in outdoor exercise activities nearby to roadways (e.g. bicycling), resulting in increased inhalation rates. However, there is a sufficient MOE for all current exposure scenarios, such that sensitive subpopulations are still unlikely to be at risk from exposure to TRWP.

Lastly, based on the marker developed by Unice, et al. (2012), Panko, et al. (2013) relied on certain assumptions when determining the concentration of TRWP in air in the different regions, including: a typical polymer makeup of passenger car tires and percent contribution of tread to TRWP. The marker developed by Unice et al. (2012) relied upon the detection of pyrolysis products from polymers found in tire tread. Specifically, one of the primary markers used is vinylcyclohexene, a pyrolysis product from styrene-butadiene (SBR) and butadiene (BR) rubbers. When determining the relationship between the detection of vinylcyclohexene and tread, it was necessary to rely upon assumptions about the market share of SBR and BR in tread. While this information was validated with a survey of tire manufacturers at the time of marker development, deviations from these assumptions could cause inaccuracies in the predicted TRWP concentrations in air reported by Panko, et al. (2013). Furthermore, in extrapolating from the measurement of the marker (which quantifies tread concentration) to TRWP concentration in air, Panko, et al. (2013) relied upon estimates of percent tread polymer in TRWP provided by Kreider, et al. (2010). Again, deviations from these assumptions could result in an over or under estimate of exposure and/or MOE.

Conclusions

Though there remain uncertainties in the risk assessment stemming from both the hazard and exposure assessments, the current weight of evidence suggests that TRWP presents a low risk to human health. Most notably, the uncertainties associated with the threshold of effect for TRWP and supporting data from other studies on tread particles or other particulate matter indicate that the benchmark used for this risk assessment is very likely to be conservative and thus tending to overestimate risk. The remaining uncertainties, be they related to hazard or exposure, could either increase or decrease the MOE. Additional data, such as more robust exposure monitoring studies or additional hazard data, to address some of the current limitations could aid in reinforcing the current assessment.

The conclusion that TRWP is unlikely to represent a human health risk is further supported by existing benchmarks established for other particulate types (e.g. diesel

exhaust) and ambient particulate. Typical ambient TRWP air concentrations are well-below the RfC for diesel exhaust, thought to be a more potent toxicant than TRWP. Furthermore, guidelines for ambient air particulate also suggest that TRWP is unlikely to represent a health risk. The annual average guideline for PM10 in ambient air is 20 $\mu g/m^3$ (WHO 2005); the average concentration of TRWP in air is 0.275 $\mu g/m^3$ (Panko et al. 2013). Collectively, these data, along with the risk assessment performed herein, suggest that TRWP is unlikely to represent a risk to human health.

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