

Climatic regulation of the neurotoxin domoic acid

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Edited by David M. Karl, University of Hawaii, Honolulu, HI, and approved November 30, 2016 (received for review April 28, 2016)

Domoic acid is a potent neurotoxin produced by certain marine microalgae that can accumulate in the foodweb, posing a health threat to human seafood consumers and wildlife in coastal regions worldwide. Evidence of climatic regulation of domoic acid in shellfish over the past 20 y in the Northern California Current regime is shown. The timing of elevated domoic acid is strongly related to warm phases of the Pacific Decadal Oscillation and the Oceanic Niño Index, an indicator of El Niño events. Ocean conditions in the northeast Pacific that are associated with warm phases of these indices, including changes in prevailing currents and advection of anomalously warm water masses onto the continental shelf, are hypothesized to contribute to increases in this toxin. We present an applied domoic acid risk assessment model for the US West Coast based on combined climatic and local variables. Evidence of regional- to basin-scale controls on domoic acid has not previously been presented. Our findings have implications in coastal zones worldwide that are affected by this toxin and are particularly relevant given the increased frequency of anomalously warm ocean conditions.

domoic acid | Pacific Decadal Oscillation | El Niño | Northern California Current | *Pseudo-nitzschia*

The Pacific Decadal Oscillation (PDO) and El Niño Southern Oscillation (ENSO) are recurring patterns of climate variability centered over the northeastern (NE) and equatorial Pacific, respectively, that fluctuate at scales of years (ENSO) to decades (PDO) (1, 2). Distinct, yet also related, these patterns can amplify or dampen each other through atmospheric teleconnection (1, 3). In the NE Pacific, they induce similar spatial patterns of sea surface temperature anomalies during positive (warm) and negative (cool) phases (4). Low-frequency physical variability attributed to the PDO and ENSO modulates large shifts in NE Pacific water temperature, ocean currents, and foodweb dynamics that can persist for months to years (2, 5, 6). Shifts in NE Pacific plankton communities occur as well (7–12); however, climate impacts on phytoplankton ecology in this region are relatively underexplored, largely due to a lack of phytoplankton data at sufficient scales.

Decadal, regional-scale monitoring of domoic acid (DA) in shellfish can be used to investigate climate-scale impacts on phytoplankton ecology. The neurotoxin DA is produced by some species of the diatom genus *Pseudo-nitzschia*. It enters secondary trophic levels when suspension feeders such as shellfish and anchovies ingest toxic *Pseudo-nitzschia* cells. Consumption of these organisms by humans can lead to a serious neurological disorder named Domoic Acid Poisoning (DAP), also termed Amnesic Shellfish Poisoning. DAP symptoms range from gastrointestinal disturbance to seizures, memory loss, or, rarely, death (13, 14).

DA was first identified as a public health threat in 1987 (15). Toxin-producing *Pseudo-nitzschia* spp. and DA have since been identified worldwide with the greatest prevalence in, and most deleterious impacts on, productive eastern boundary upwelling systems (16). Laboratory experiments have found multiple factors that can up- or down-regulate cellular DA synthesis, but

there is no consensus regarding whether any one factor or combination of factors lead to predictable DA production in situ (16, 17). DA regulation has primarily been investigated using field observations of discrete bloom events and laboratory-based experiments (17). With some exceptions (e.g., ref. 18), the majority of these studies are based on temporally short or spatially small datasets relative to climate-scale indexes. To protect public health, DA in shellfish has been monitored along the US West Coast since 1991 (19). These records are now long enough to investigate DA regulation at the temporal-spatial scales associated with NE Pacific climate events that have occurred in recent decades, such as El Niño events, PDO transitions, and the 2013–2015 NE Pacific Warm Anomaly (20, 21).

Our research expands on observations of climate-scale regulation of plankton in the Oregon (OR) coastal region of the NE Pacific (e.g., refs. 8–10 and 22). The presence/absence of unique copepod communities is strongly correlated with the PDO (7, 23) and El Niño events (8). Copepods are a robust indicator of water mass transport to the continental shelf off of OR and the strength of the Northern California Current (NCC) (9, 24, 25), a strong seasonal current along the US West Coast. We investigate the relationship between low-frequency climate signals and a 20-y record of DA levels in OR razor clams, then apply these findings to test whether DA levels in Washington (WA) and California (CA) shellfish are also related to warm regimes.

Materials and Methods

Basin-Scale Indices of Warm/Cool Ocean Conditions. The PDO is a monthly proxy of climate variability based on North Pacific sea surface temperature (SST) variability. The Oceanic Niño Index (ONI) is a monthly index based on equatorial Pacific SST anomaly values. A threshold of ± 1 °C separates moderate to strong El Niño (warm) events from weak ones. Both indexes were acquired for 1991–2015 (*SI Materials and Methods*).

Significance

We investigate regulation of domoic acid, a potent marine phycotoxin, at the climate scale. Due to the threat domoic acid can pose to public health, marine wildlife, and coastal economies, decades of laboratory experiments have examined controls on domoic acid production without reaching consensus on reliable toxin-producing conditions. Our findings reveal an association between domoic acid in shellfish and climate-scale warm ocean conditions, a unique, large-scale perspective relative to previous work.

Author contributions: S.M.M. and A.E.W. designed research; S.M.M., A.M.W., V.L.T., M.H., and A.E.W. performed research; W.P. and A.E.W. analyzed data; and S.M.M. wrote the paper.

The authors declare no conflict of interest.

This article is a PNAS Direct Submission.

Freely available online through the PNAS open access option.

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This article contains supporting information online at www.pnas.org/lookup/suppl/doi:10.1073/pnas.1606798114/-DCSupplemental.

Local (OR) DA Values and Indices of Warm Ocean Conditions. DA levels in OR razor clams (*Siliqua patula*) have been monitored coastwide by the OR Department of Agriculture every 2 wk to 4 wk from 1992–2015 (19, 26). These data were binned to coastwide monthly DA maxima. The closure threshold for shellfish harvesting is DA in shellfish tissue of ≥ 20 parts per million (ppm). Depuration of DA by razor clams can take months to a year (27–29), complicating efforts to define discrete “DA events.” To aid in deconvolving events, two metrics were defined: (i) “DA event onset,” or the beginning of an event, conservatively defined as the first date that DA values surpassed 20 ppm with no prior incidences of DA above 20 ppm in the previous 12 mo; and (ii) “annual DA maxima,” or the maximum DA value above 20 ppm reached each year; this captures DA events that can occur during prolonged depuration and also describes when the most toxic values occur each year. If a DA maximum occurred in January or February and then decreased, it was assumed to represent toxin depuration and omitted; if a peak (defined as at least 3 mo of an upward trend in monthly DA above 20 ppm) occurred later that year yet was less than this depuration-based maxima, it was assigned as the annual maxima.

Two copepod community metrics were derived from roughly fortnightly zooplankton sampling at 44.65°N, 124.30°W, 5 nautical miles (nm) offshore (west) of Newport, OR, from 1996–2015: the annual date of the “biological spring transition” and the monthly copepod species richness (CSR) anomaly. The former is a seasonal proxy, the first year–day the copepod community transitioned from warm-water (southern/offshore) species assemblages typical of winter to cold-water (northern) summer assemblages (23). The CSR anomaly is a monthly proxy of the number of copepod species present; more species are indicative of warmer water masses. See also *SI Materials and Methods*.

Average alongshore current measurements for March–April were calculated from acoustic Doppler current profiler deployments at 44.65°N, 124.31°W, 10 nm offshore of Newport, or high-frequency radar current mapping observations from shore (10).

SST was measured at 0.6 m below the surface at the National Data Buoy Center mooring station 46050 near 44.65°N, 124.53°W, 20 nm offshore of Newport. A monthly SST anomaly index was calculated as the difference between monthly average SST and the 1992–2015 climatological mean for each month. Annual mean water temperatures for December through March were also obtained for Yaquina Bay, an estuary in Newport (10).

The OR coastal region is an eastern boundary upwelling regime, with an annual upwelling season (April–October) characterized by net northerly winds and offshore currents that lead to increased nutrients and phytoplankton biomass. Downwelling season (November–March) is typified by net southerly winds, onshore movement of water, and low biomass. The cumulative upwelling index describes the annual dates that these seasons begin, based on the cumulative northerly wind stress observed at Newport each year (damp.coas.oregonstate.edu/windstress/index.html) (26).

Cross-Correlation and Regression Analyses. Cross-correlation was conducted for 1996–2015 (MATLAB code at <https://github.com/smmckib/crosscorr>); any gaps in sampling data were interpolated. March PDO and ONI values were regressed against annual-scale physical and biological parameters. March was chosen because it is representative of the conditions leading into upwelling season.

West Coast Risk Assessment. A risk analysis model was developed for the West Coast to evaluate whether parameters associated with elevated DA in OR also applied to elevated DA in WA and CA shellfish, to the north and south of OR. Our goal was to develop a basic, applied model that can be easily created and interpreted by both scientists and nonscientists. We selected publicly available parameters and an additive method to evaluate risk, allowing others to use the model without the need for specialized datasets or statistical tools.

Model parameters. In WA, DA sampling of razor clams (wdfw.wa.gov/fishing/shellfish/razorclams/domoic_levels.html) occurred every 2 wk (September–May) or 4 wk (June–August) from 1991–2015. DA levels in CA shellfish (www.cdph.ca.gov/HealthInfo/environmentalhealth/water/Pages/Shellfish_reports.aspx) from 2000–2015 were available as weekly maxima detected at various sites. If values were reported as a discrete range, they were converted to continuous values: 1 ppm to <20 ppm = 10 ppm; ≥ 20 ppm = 50 ppm. CA data included mussels (63%), razor clams (17%), oysters (14%), and other shellfish (6%, e.g., scallops). DA analyses were performed only when blooms of *Pseudo-nitzschia* were detected. Liquid chromatography with UV absorbance detection was used to determine DA levels in WA (30) and CA (31) shellfish tissue. DA data were binned into monthly maxima and annual maxima over eight latitude bins based

on hydrography and sampling frequency: southern CA (32°N to 34°N); south central CA (34°N to 36°N); central CA (36°N to 39°N); northern CA (39°N to 42°N); southern OR (42°N to 44°N); central OR (44°N to 45°N); northern OR (45°N to 46.3°N); and WA (46.3°N to 48°N). Monthly average coastal upwelling indexes were obtained from the Pacific Fisheries Environmental Laboratory (<https://www.pfeg.noaa.gov/products/PFEL/modeled/indices/upwelling/upwelling.html>) for 32° to 48° latitude. These data are based on geostrophic winds derived from monthly mean surface atmospheric pressure fields. Negative values represent the intensity of large-scale, wind-induced coastal upwelling. Data were linearly interpolated from increments of 3° latitude to increments of 1° latitude. Daily SST values based on satellite and in situ data (32) were obtained from the National Oceanic and Atmospheric Administration (NOAA) Environmental Research Division’s Data Access Program (coastwatch.pfeg.noaa.gov/erddap/griddap/ncdcOisst2Agg.html) for the West Coast (32°N to 48°N) from 1991–2015. SST anomaly values over a 1° (north–south) by 0.5° (east–west) bin near the coast were derived from these data (*SI Materials and Methods*).

Risk assessment model. Positive PDO, ONI, and SST anomaly, and upwelling conditions, were assigned as proxies of DA risk. These data were compiled for 1991–2015 between 32°N and 48°N at 1° increments. The PDO, ONI, and SST anomaly data were first reduced to include only values of >0 (warm). Each parameter was then divided by its maximum value during 1991–2015, scaling all to a common range (0 to 1). The maximum ONI value observed each winter was also determined. If the value was ≥ 1 (moderate to strong El Niño), then the maximum was propagated to each month of the following upwelling season. If upwelling conditions were present (negative value), then the four scaled variables (PDO, ONI, SST anomaly, and the maximum prior winter ONI) were summed to yield a monthly indicator of risk for elevated DA.

Risk values were compared with DA events and defined for model assessment as the annual DA maxima from each of the eight latitudinal bins. The annual maximum risk value and the risk value during the month the DA event occurred were both regressed against the annual DA maxima for each bin. Model predictions of the frequency of “expected” DA events relative to the “observed” frequency were tallied. If risk values for any latitude were positive for three consecutive months in any given year per bin, that year was expected to experience closure levels of DA. Relationships between upwelling and DA events were quantified separately from risk assessment: (i) the sum of the PDO + ONI in March of the corresponding year was regressed against annual DA maxima, and (ii) the number of annual maxima occurring during upwelling season through 1 mo following the season were tallied. The two southern CA bins were omitted, as upwelling-favorable conditions span much, or all, of the year.

Results

Warm PDO phases occur between 1996–1998, 2002–2006, 2009–2010 and January 2014–2015 (Fig. 1A). The ONI and PDO are highly correlated with zero lag (Table S1). Moderate to strong El Niño and La Niña events coincide with warm to cool transitions, respectively, of the PDO (Fig. 1A). The local SST anomaly (Fig. 1B) is highly correlated with PDO and ONI at zero lag, with a slightly stronger relationship to the PDO (Table S1).

In OR, six DA events occurred between 1996 and 2016 (Fig. 1): 1996, 1998–1999, 2001, 2002–2006, 2010, and 2014–2015. All were preceded by or coincident with positive PDO values, and three were preceded by or coincident with positive ONI values. The shift to a positive CSR anomaly (Fig. 1C and D) lags warm shifts in the physical indices (Fig. 1A and B) by 0 mo to 9 mo (Table S1). During warm phases, the annual spring biological transition date occurs at an average to later than average time and occurs earlier than average in cool phases (Fig. 1D). DA maxima in 2003–2005 suggest events happened each year during the prolonged 2002–2006 event.

The onset of DA events and the annual DA maxima typically occur in association with upwelling season (Fig. 1D and E). Event onset in 1996, 1998, 2010, and 2015 and annual DA maxima in 1996, 2001, 2010, and 2004–2006 occurred during the upwelling season. Event onset in 2002 and 2014 and annual maxima in 1998, 2002, 2014, and 2015 occurred near the end of, or the month after, the upwelling season. The 2001 event was not

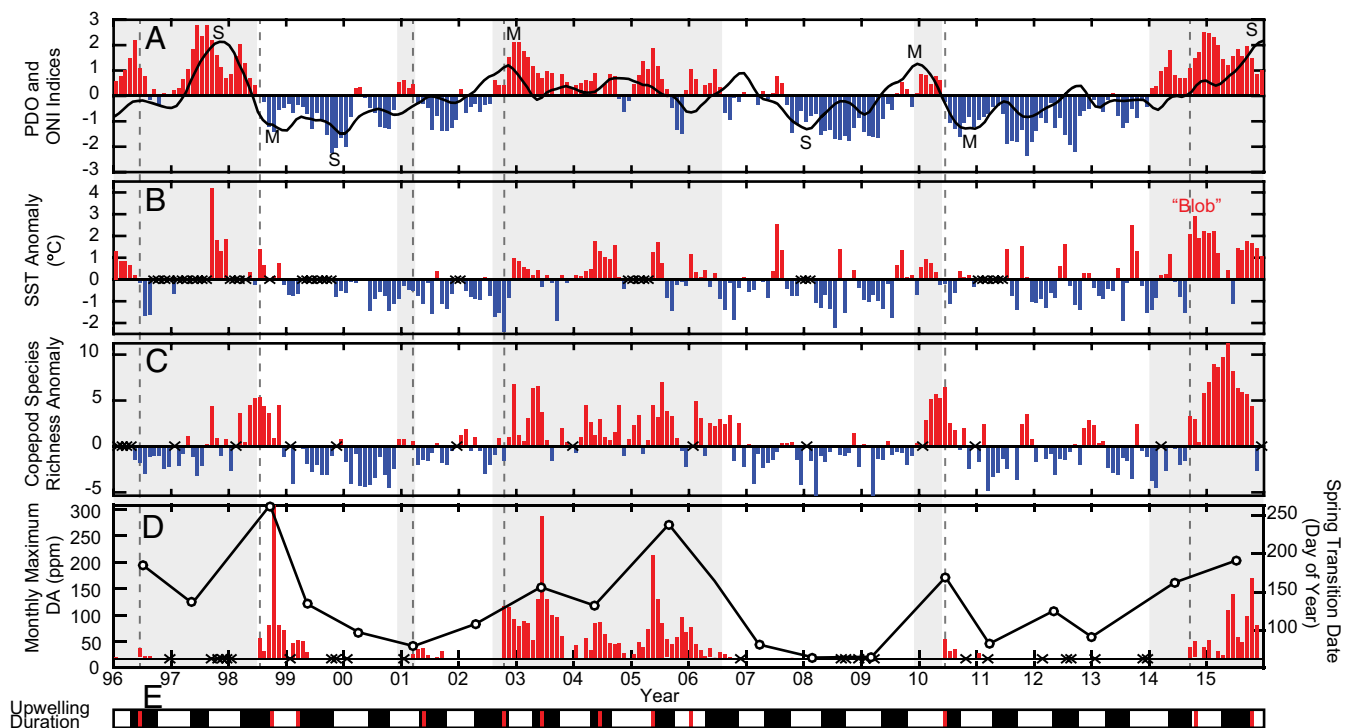


Fig. 1. (A) Warm and cool ocean regimes, (B) local SST anomaly, and (C and D) biological response. (A) PDO (red or blue vertical bars) and ONI (black line) indices; strong (S) to moderate (M) El Niño (≥ 1) and La Niña (≤ -1) events are labeled. (B) SST anomaly 20 nm off central OR. (C) The CSR anomaly 5 nm off central OR. (D) Monthly OR coastal maximum DA levels in razor clams (vertical bars); horizontal black line is the 20-ppm closure threshold; data below 20 ppm are not shown. Black line in D shows the spring biological transition date (right y axis). (E) Black boxes indicate the duration of upwelling season each year; red vertical bars indicate the timing of annual DA maxima in relationship to upwelling. Gray shaded regions are warm regimes based on the PDO. Dashed vertical lines indicate onset of the six major DA events. The September 2014 arrival of the NE Pacific Warm Anomaly (colloquially termed “The Blob”) to the OR coastal region is labeled on B. “X” symbols along the x axes indicate that no data were available for that month (B–D).

associated with the upwelling season; maxima in 1999 and 2006 were likely depuration.

At annual scales, nearly all physical and biological parameters were significantly, positively correlated with March PDO and ONI values: higher estuarine water temperature, more positive CSR and SST anomalies, weaker southward alongshore currents, later biological transition date, and a higher annual maximum DA (Table S2). Most parameters had a stronger statistical relationship with the PDO than with the ONI (Table S2). Exceptions were CSR and DA values, which were about equally related to the March PDO and March ONI. Maximum annual DA is also significantly and positively correlated to these proxies of warm conditions, with the exception of direction of alongshore currents (Table S2).

The sum of the March PDO and ONI is a stronger predictor of warm biological and physical conditions than either index alone (Fig. S1 and Table S2). The exception is average alongshore currents, which were only significantly related to the March PDO. For all regressions, the five highest annual DA values corresponded to the warmest conditions (Fig. S1). The year 2002 consistently fell lower than predicted by these regressions (Fig. S1); DA was the fifth highest on record, but PDO and ONI conditions were cool to neutral in March. The 2002 DA maximum occurred in October, largely coincident with an abrupt late-year shift in all indexes to warm conditions during the onset of an El Niño event.

Risk model output and monthly DA values show latitudinal variability in DA, event risk, and upwelling phenology in OR and WA (Fig. 2) and in CA (Fig. S2). False positives range from 0 to 50% (Table S3). The model did not predict the high DA levels observed in 2001 in WA and northern and central OR (Fig. 2), or in 2011 in southern CA (Fig. S2). Regressions of annual max-

imum DA with both model values (annual maximum and value during month of DA onset), as well as the March PDO + ONI value, show significant, positive correlations (Table S4). Statistical outliers (2007 and 2011 in southern CA, and 1992 in southern OR) were not included in these regressions. Comparison of Fig. 2 and Fig. S1 also shows differential expression of DA in routinely sampled OR and WA razor clams (Fig. 2) compared with event-based sampling of predominantly mussels in CA (Fig. S1).

Discussion

Our observations indicate that OR DA events occur during warm ocean regimes due to conditions that favor advection of anomalously warm water masses from southern or offshore locations onto the continental shelf. In warm years, the following are seen: (i) The spring biological transition date, indicative of the seasonal transition of the NCC to southward flow, is later; (ii) alongshore currents tend to be weaker in association with warm PDO values; (iii) estuarine and offshore water temperatures are elevated; (iv) the CSR anomaly is positive, showing a planktonic regime shift to copepod species of a predominantly offshore/southern origin; and (v) DA levels in OR coast razor clams surpass closure threshold values.

A series of associations, from basin to regional scale, explain DA transport and elevated levels in shellfish. The DA events along the OR coast are a result of low-frequency variability in climate-scale forcing modulated by local conditions (upwelling season). The PDO and ONI indicate when the NE Pacific may experience warm conditions, and local factors such as copepod community composition and offshore and estuarine water temperatures collectively describe whether warm water masses and their endemic plankton communities have reached the

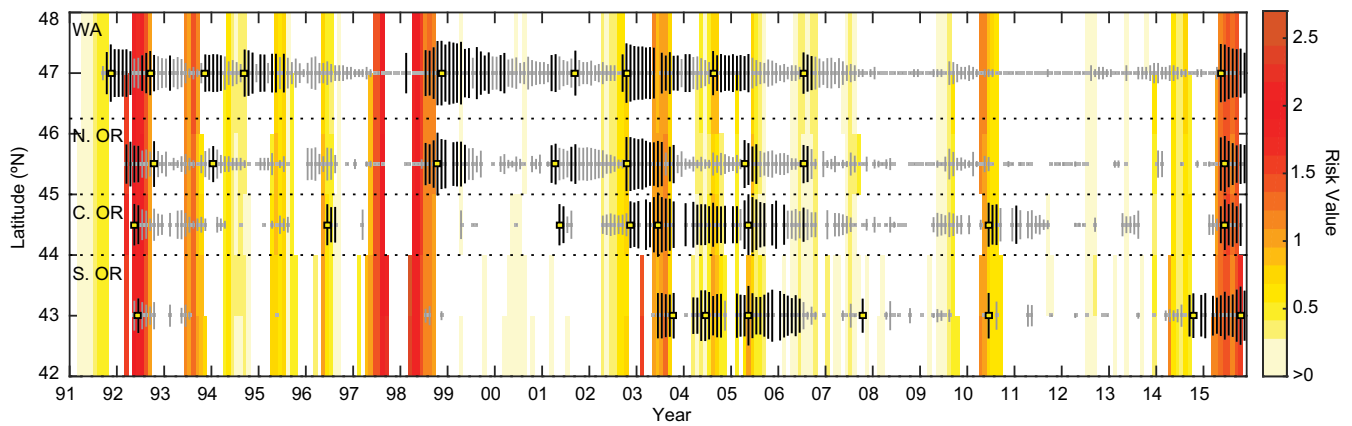


Fig. 2. DA risk analysis model output (yellow to red) and DA levels in OR and WA razor clams (vertical bars) from 1992–2015. Model values indicate increased risk of elevated DA based on proxies of warm ocean parameters; model values are only calculated during upwelling season, when concentrations of phytoplankton are likely to be greatest each year. White regions indicate that elevated DA is least likely, as the model equals zero and/or it is downwelling season. From top to bottom, monthly maximum DA values (vertical bars) are latitudinally binned as follows: WA (46.3°N to 48°N), northern OR (45°N to 46.3°N), central OR (44°N to 45°N), and southern OR (42°N to 44°N). Bar length is proportional to the monthly maximum DA value. Color indicates DA \geq 20 ppm (black lines), from 1 to <20 ppm (gray lines), or not detected (gray squares). An absence of points indicates no DA data available. Annual DA maxima used in model evaluation are highlighted with yellow squares. Results of model evaluation are shown in Tables S3 and S4. See Fig. S2 for CA risk analysis.

nearshore zone of the OR continental shelf waters. The phenology of upwelling season and the spring biological transition modulate when conditions are most favorable to phytoplankton blooms and which plankton communities are present, respectively. Warm conditions leading into the upwelling season (PDO + ONI in March) are indicators of the annual magnitude of DA toxicity and spring transition date. Seasonal termination of upwelling winds in late summer/autumn may coincide with the onset (2002, 2014) or annual maxima (1998, 2015) of DA events. Shorter-term wind relaxation/reversal events (weeks) transport toxic blooms to the intertidal zone, where they are ingested by shellfish (22, 26) and may be responsible for the annual DA maxima observed during warm-phase upwelling seasons. Two categories of potential mechanisms behind these relationships in the context of our observations and relevant literature are discussed in *Changes in Water Masses and Circulation During Warm Regimes* and *Cellular-Level Drivers of DA Production*.

Changes in Water Masses and Circulation During Warm Regimes.

Evidence linking basin-scale physical changes in ocean circulation to plankton is well constrained in the OR coastal region. The planktonic copepod community off the central OR coast is a robust indicator of PDO- and ONI-related shifts in the source waters that feed the NCC (7, 8, 23). Negative (cool) PDO phases favor the influx of cooler waters into the NCC from the north, delivering zooplankton assemblages to coastal OR that are dominated by larger, lipid-rich subarctic copepods with lower species richness. In contrast, positive (warm) PDO phases favor poleward transport and onshore intrusion of subtropical oceanic waters (24), so smaller, lipid-poor subtropical copepod communities with higher species richness are dominant. Climate-scale warm ocean conditions are also conducive to the transport, and successful recruitment, of planktonic European green crab larvae (*Carcinus maenas*) into OR estuaries (10). This invasive species is found in low numbers during cool regimes; however, annual recruitment success is greatly increased when the PDO is positive, SST is warmer, and the biological spring transition is later (10). Annual DA maxima in OR razor clams are significantly and positively correlated with annual green crab recruitment strength in OR [Yamada et al. (10), table 2] from 1998–2014 ($r^2 = 0.49$, $P < 0.002$), suggesting that similar conditions may lead to both crab success and elevated DA in razor

clams. For example, crab success was increased by both onshore transport and nearshore retention of the larvae in OR estuaries (10). Assuming the presence of a toxigenic bloom, blooms would also promote elevated DA in shellfish through transport into, and prolonged retention within, the intertidal and subtidal zones where phytoplankton are ingested by the shellfish. In sum, warm water copepod communities, green crab recruitment success, and DA in shellfish are all positively correlated with warm regimes. These seemingly disparate factors share one thing in common—a dependence on organisms that are meroplankton (crab larvae) or holoplankton—and hence are indicators of water mass transport during oscillations between warm and cool regimes.

Cellular-Level Drivers of DA Production. There are at least two potential hypotheses to connect physical conditions during warm regimes, *Pseudo-nitzschia* communities, cellular DA production, and elevated DA in OR razor clams: (i) “Warm water” *Pseudo-nitzschia* assemblages that are more likely to produce DA are advected into the region from offshore or southern waters due to circulation changes during warm phases. (ii) Environmental conditions during warm phases lead to up-regulation of DA synthesis in resident populations. These explanations need not be mutually exclusive. The 2002 and 2014 DA events support the former hypothesis; they occurred during years with initially cool ocean conditions that abruptly shifted to warm conditions during, or just after, the annual transition from upwelling to downwelling season. Following the 2002 event, both elevated DA and warm conditions persisted through 2006, along with the warm PDO. In 2014, the DA event began coincident with the arrival of the NE Pacific Warm Anomaly on the OR coast. This strongly positive temperature anomaly, the greatest observed in the region since the 1980s, was identified in the Gulf of Alaska during the winter of 2013–2014 (21) and expanded to much of the NE Pacific by 2015. In mid-2014, the warm anomaly was held offshore of OR by upwelling-favorable winds (33). Downwelling season initiated in mid-September; winds reversed, the warm waters moved shoreward, and central OR coast SST rose 8 °C over a period of just 31 h (33). This same month, the 2014 DA event began and the SST and CSR anomalies became positive (Fig. 1).

In contrast, the 1998 and 2010 DA events and CSR lagged strong, coincident warm-to-cool transitions in the PDO and ONI (Fig. 1). These events support the hypothesis that

up-regulation of DA, and/or enhanced growth of toxigenic *Pseudo-nitzschia* is favored during the transition from warm to cool regimes. Warm ocean regimes potentially affect *Pseudo-nitzschia* species abundance and toxicity in an array of ways, from cellular and metabolic processes that are sensitive to elevated temperatures to larger-scale changes in phenology, water column structure, and circulation patterns (27, 34). The linkages between DA production and environmental factors such as macronutrients, trace metals, temperature, and salinity are also complex and variable (16). It is likely the case that no one single environmental variable is a strong predictor of DA (27); hence a mechanistic explanation behind cellular-level DA production and elevated DA in shellfish during warm ocean regimes is outside the scope of this study given the data we have. Even so, our findings frame future work investigating DA production by *Pseudo-nitzschia* in the context of conditions associated with warm regimes, for example, monitoring changes in species composition over time to investigate whether distinctive “warm” *Pseudo-nitzschia* assemblages indeed cooccur with copepod community shifts. More data are also needed to evaluate how regional-scale controls (stratification, nutrients, etc.) change during warm-ocean regimes and potentially increase in situ DA production.

Broad-Scale Implications. Positive climatic indexes and local SST anomalies, as well as upwelling conditions, were found to be indicators of OR DA events; whether these indicators applied to DA events along the broader NCC was subsequently tested using a risk assessment model for the US West Coast. False positives in the model were up to 50% and as low as 0%. The higher values are due, at least in part, to the long-term depuration time of razor clams and resulting conservative definition of a DA event. This potentially skewed false positive calculations high. For example, false positives were greatest in WA: In 2009, a peak in DA occurred, but it was below the 20-ppm threshold and not considered a DA event for that year (Fig. 2); in 2007, DA levels increased for the first several months but were subthreshold. There were also annual maxima not detected by the model in 2001 from WA to central OR. In OR, this event occurred in association with a short, positive shift in the PDO and CSR (Fig. 1); however, it was during the downwelling season, and hence not detected by the model. A maximum was also missed in southern CA in 2011 (Fig. S2). The rationale for this omission is unclear but may be related to local-scale regulation of DA events (discussed in *Extreme Warming Events*). Even with these exceptions, the model has a significant success rate, and absolute risk values were strongly correlated to measured monthly and annual DA (Table S4).

Extreme Warming Events. When warm PDO conditions and El Niño events coincide, their positive SST anomalies are approximately additive (1); coincidence of El Niño and warm PDO conditions typically yield the most classic signatures of an El Niño event in North America (3, 4, 35). As such, concurrently positive PDO and ONI indices lead to periods of more extreme warming in the NE Pacific relative to when one or the other is positive. Our OR results support this: The summed March PDO + ONI value was typically more significantly related to environmental indicators of warm ocean conditions than either index alone; the greater the March PDO + ONI, the warmer the conditions and the greater the DA levels.

If basin-scale warming events regulate DA events in OR, it follows that DA levels may be elevated by these events in nearby CA and WA as well. Our results (Fig. 2, Fig. S2, and Tables S3 and S4) and previous work collectively indicate that extreme warm phases (positive PDO concurrent with a strong to moderate El Niño) promote DA events along the West Coast that span two to three contiguous states. Since 1991, five extensive warming

events have occurred: 1991–1992, 1997–1998, 2002–2003, 2009–2010, and 2015–present. DA surpassed 20 ppm in shellfish in two to three contiguous states during time frames associated with all of these warm phases: late 1991–1992 (WA, OR, and CA) [Lewitus et al. (19) show DA over 20 ppm in late 1991, but these data were not available on the CA Department of Health’s website for this study]; 1998–1999 (WA and OR); 2002–2003 (WA, OR, and CA); 2010 (OR and CA); and 2015 (WA, OR, and CA). The most latitudinally extensive DA events initiated when the highest risk values occurred (values of >1). The 1991, 1998, and 2010 events were described as the most “exceptional and widespread” West Coast occurrences of DA between 1991 and 2010 (19). In OR and WA, the 1991–1992, 1998–1999, and 2002–2003 events caused significant economic losses (19, 28, 36, 37) due to closures of razor clam and Dungeness crab (WA only) fisheries. In 2010, shellfish closures occurred in OR and CA (Fig. 2 and Fig. S2), and DA reached record highs in CA mussels and lobster (19); high DA was detected in coastal waters from at least central CA north to central OR (26). In 2015, extensive NE Pacific warming coincided with an unprecedented, record-setting DA event from CA to WA (20, 38).

Variability among DA events in WA, OR, and CA is also evident. Maximum DA in CA mussel tissue is higher (610 ppm) than in OR or WA razor clams (295 ppm) (19), and DA has exceeded 20 ppm in CA shellfish and other seafood species (sardines, anchovies) (19) nearly every year since 2000. Documented cases of DA in marine birds and mammals predominantly occur in CA (17). These differences in CA relative to OR or WA may be due to differing distributions of planktivorous shellfish and finfish affected by DA, differing sampling methods and frequencies, and/or greater incidence of toxigenic *Pseudo-nitzschia*. If the latter is indeed a factor, it suggests the potential for “seeding” populations moving northward during warm ocean regimes. Several retentive areas (e.g., Heceta Bank and the Juan de Fuca Eddy) are conducive to phytoplankton bloom initiation, including toxigenic *Pseudo-nitzschia* (39–41). Northward advection during warm regimes may be a source of toxic blooms to these regions. Also, latitudinal variability among the three states depends on a number of subclimate-scale processes; this may explain inaccuracies in the risk assessment model. For example, in 2010, a DA event did not occur in northern OR or WA but did occur farther to the south, yet the model was positive for the entire region. The Columbia River Plume may have halted northward advection of the toxigenic bloom (42). These processes will be important to consider in future regional-scale model application.

Conclusions

We present evidence for climate-scale regulation of shellfish DA in the NCC. Even with the large potential for differences among WA, OR, and CA, our observations reveal a common relationship: The warmer the ocean conditions, the more likely DA is to surpass alert thresholds during upwelling season, and the more toxic and/or more widespread a DA event has the potential to become. The risk parameters presented in this work as indicative of elevated DA in shellfish (positive PDO, ONI, and local SST anomaly values, and upwelling conditions) can be applied to future examination of relationships between warm regimes and DA along the West Coast, as well as other eastern boundary currents worldwide. If these warm ocean regimes become more persistent due to global warming, as some hypothesize, West Coast DA events may also increase in persistence and frequency.

ACKNOWLEDGMENTS. We thank Dr. Stephen Pierce for the upwelling data and Dan Ayres for providing the WA shellfish data. This study was supported by NOAA Grant NA07NOS4780195 (to A.E.W., W.P., A.M.W., and M.H.) from

the Monitoring and Event Response for Harmful Algal Blooms (MERHAB) program. Additional support was provided by the National Science Foundation Grant 1459480-OCE (to A.E.W.). This is MERHAB Publication 190. The

statements, findings, conclusions, and recommendations are those of the authors and do not necessarily reflect the views of NOAA or the Department of Commerce.

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