Sequestering and Biotransformation of Paralytic Shellfish Toxins in Scallops: Food Safety Implications of Harvesting Wild Stocks and Aquaculture Biotechnology

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Introduction

Marine toxins of algal origin (phycotoxins) are a diverse group of biologically active compounds with high acute human toxicities. The neurotoxins involved in paralytic shellfish poisoning (PSP) (**Figure 1**) are the most potent biotoxins known to accumulate in scallops. While scallops are not frequent causes of PSP in North America, illnesses and even deaths have been attributed to the consumption of whole sea scallops (*Placopecten magellanicus*) (Medcof et al. 1947; Washington Office of Public Health Laboratories and Epidemiology, unpublished, 1978), purple-hinge rock scallops (*Crassadoma gigantea* = *Hinnites multirugosus*) (Sharpe 1981), and pink (*Chlamys rubida*) and spiny (*Chlamys hastata*) scallops (Department of Fisheries and Oceans 1989). Infrequent deaths due to PSP toxins accumulated in scallops are also recorded from Asian countries, specifically from the Philippines and Japan (Estudillo and Gonzales 1984; Nomata, pers. comm.).

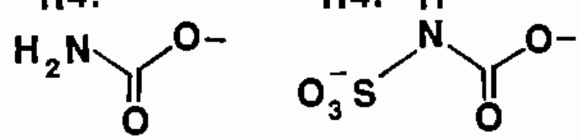
Bivalve shellfish, including scallops, sequester PSP toxins in their tissues through filter-feeding upon toxic pelagic and benthic microorganisms (Shumway, Selvin and Schick 1987). The microorganisms responsible for PSP in temperate waters are most often members of the cosmopolitan dinoflagellate genus *Alexandrium* (known also as the *Protogonyaulax catenella/tamarensis* species complex), or, less frequently, are of the chain-forming species *Gymnodinium catenatum* (Taylor 1984, Shimizu 1987). In areas where *Alexandrium* blooms are regular events, such as in North America and Japan (Nishihama 1980, Ogata et al. 1982, Gillis et al. 1991), the risk of PSP has had a markedly depressive effect on the scallop industry.

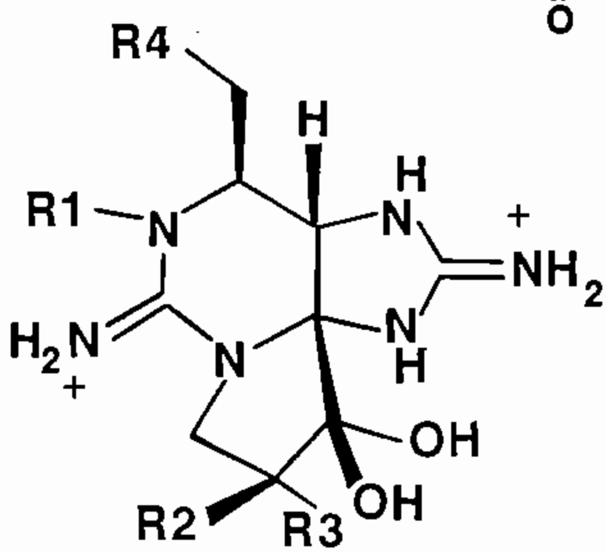
Figure 1

Structures of PSP toxins found in shellfish species, including carbamate, N-sulfocarbamoyl, and decarbamoyl derivatives

Saxitoxin = STX; neosaxitoxin = NEO; gonyautoxins 1,2,3,4 = GTX1,2,3,4

R1	R2	R3	Carbamate Toxins	N-Sulfocarbamoyl Toxins	Decarbamoyl Toxins
H	H	H	STX	B1	dc-STX
OH	H	H	NEO	B2	dc-NEO
OH	H	OSO_3^-	GTX 1	C3	dc-GTX 1
H	H	OSO_3^-	GTX 2	C1	dc-GTX 2
H	OSO_3^-	H	GTX 3	C2	dc-GTX 3
OH	OSO_3^-	H	GTX 4	C4	dc-GTX 4
			R4:	R4:	R4: HO−





Food safety regulations and the utilization of scallop resources

Major commercial fisheries are dependent upon wild scallop populations, and aquaculture of selected stocks is an increasingly important component of exploited marine food species (see Hardy 1991, Shumway 1991 and references therein). Scallop aquaculture and harvesting of wild stocks are frequently carried out in areas where toxic algal blooms are chronic seasonal events (Shumway 1990, 1991). In spite of such toxic occurrences, scallops have not always been included in PSP monitoring programmes, since in North America only the adductor muscle is usually consumed. However, in certain other countries, including Japan, Australia, and European nations, scallops with attached gonads ("roe-on") are a popular seafood. In the United States, the regulations of the Interstate Shellfish Sanitation Conference (ISSC) have only recently been applied to scallops.

Efforts to intensify scallop aquaculture in areas prone to toxic blooms, and the expanded international trade in whole and "roe-on" scallops, have provoked public health concerns regarding the safety of this important resource (Nishitani and Chew 1988, Ahmed 1991, Gillis et al. 1991). The National Marine Fisheries Service (NMFS) and the Food and Drug Administration (FDA) in the United States, and the Inspection Branch of the Department of Fisheries and Oceans in Canada, are currently developing a certification scheme for "roe-on" and whole scallops. The exploitation of scallop resources will remain severely restricted until this regulatory issue is resolved.

PSP toxin accumulation and detoxification in scallops

The Georges Bank region of the northwest Atlantic coast (40-43° N 66-70° W), partitioned into American and Canadian fishing sectors, is a rich harvesting ground for sea scallops (*Placopecten magellanicus*). Bourne and Read (1965) long ago advocated the marketing of scallops from Georges Bank with gonads and mantles attached to the adductor muscle. However, the discovery of high PSP toxicity in scallops from the American sector (White et al. 1993a), and recent closures of most of the Canadian sector to "roe-on" fishing, due to PSP toxin levels in excess of the regulatory limit (80 µg STXeq/100g shellfish tissue) (Gillis et al. 1991), have made this a tenuous proposition.

Previous field studies based upon mouse bioassay data have shown that PSP toxin levels in scallops vary both seasonally and according to geographical location (Bourne 1965, Jamieson and Chandler 1983). Problems associated with monitoring scallops for PSP toxicity have been further exacerbated by high variability in toxicity among individual specimens from the same location (Gillis et al. 1991, White et al. 1993b). Jamieson and Chandler (1983) noted that PSP toxicity in scallops from the Bay of Fundy in eastern Canada peaked during fall and winter, when no toxic *Alexandrium* blooms were evident. This toxicity variation is undoubtedly due to a combination of factors, including the timing, persistence and magnitude of toxic blooms, the specific toxicify per cell and toxin composition of the contaminating organism, environmental effects on scallop metabolism, and perhaps genotypic differences among scallop populations.

Among filter-feeding bivalve molluscs, scallops can be classified with species capable of prolonged retention of PSP toxins, for periods ranging from months to years (Medcof et al. 1947, Jamieson and Chandler 1983, Shumway, Sherman-Caswell and Hurst 1988); certain tissues, including the digestive gland and mantles, can remain toxic year-round (Bourne 1965, Shumway,

Sherman-Caswell and Hurst 1988). Hypotheses advanced to explain chronically high PSP toxin levels in scallops, even throughout the winter, include: i) reduced basal metabolism and filtration activity in colder waters; ii) toxin bioconversion to more toxic derivatives; iii) the presence of cryptic sub-surface blooms of toxic dinoflagellates; and iv) the ingestion of toxic benthic resting cysts (hypnozygotes) which accumulate and overwinter in the sediments.

Spatio-temporal variation in the accumulation, biotransformation and elimination of PSP toxins by sea scallops from stations in the Gulf of Maine was studied in detail in 1988-89 (Cembella and Shumway 1991). The PSP toxin composition and tissue-specific toxin concentration were determined on a weekly basis (except in winter) for replicate (n=6) individuals from an offshore (80 m depth) and an inshore (20 m depth) station, using high-performance liquid chromatography with fluorescence detection (HPLC-FD) (Sullivan and Wekell 1986) (**Figure 2**).

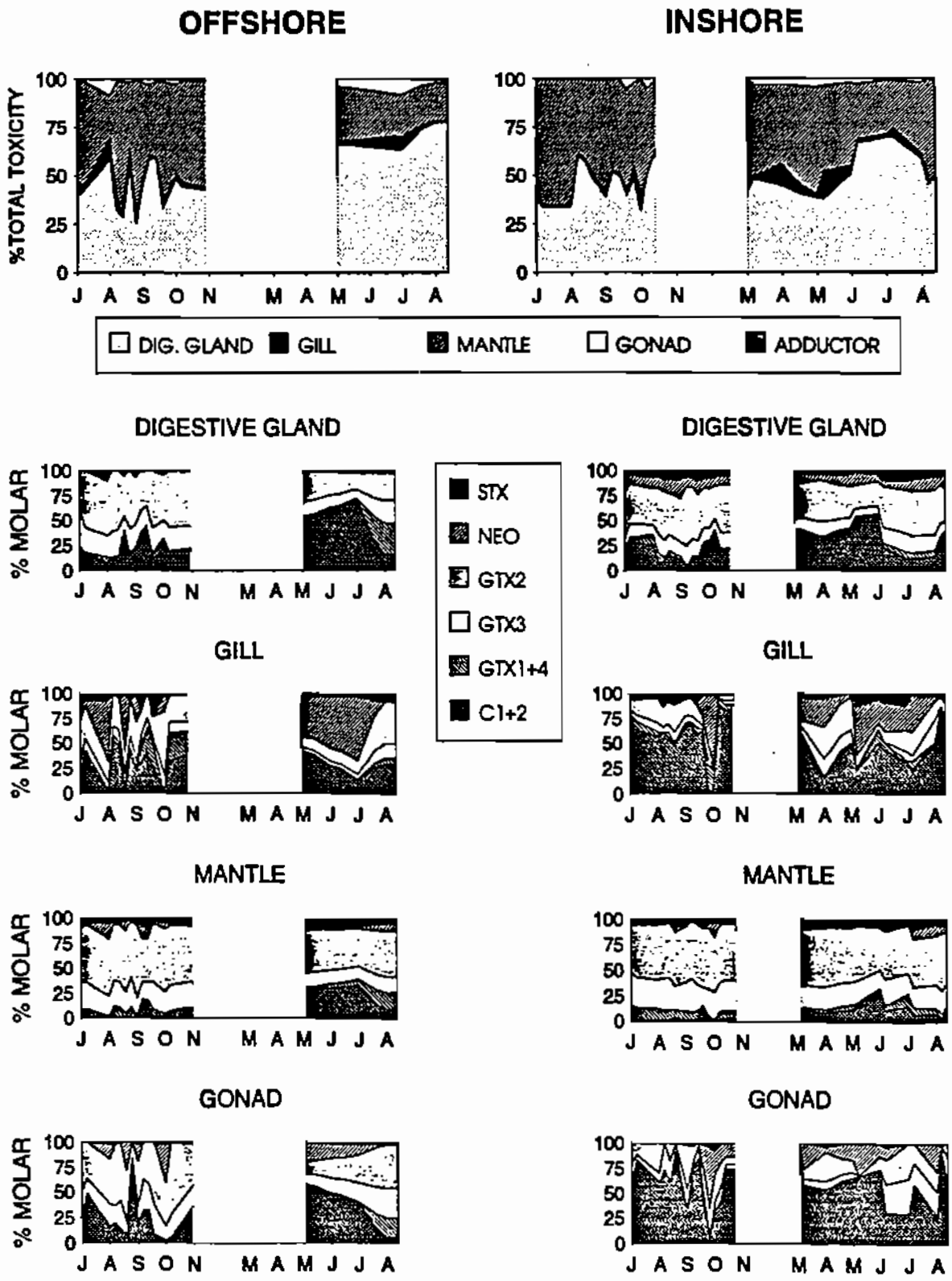
As a general rule, the contribution of various tissue compartments to total scallop body burden of PSP toxins in *Placopecten*, as determined by the AOAC mouse bioassay, is as follows (in decreasing order of importance): digestive gland (hepatopancreas, liver) > mantle (rims) > gill > gonad (roe) > adductor muscle (Bourne 1965, Watson-Wright et al. 1989). Despite seasonal fluctuations, this pattern was substantially confirmed in the HPLC analysis of inshore and offshore populations of *P. magellanicus* (Figure 2), although, on a weight-specific basis, PSP toxicity in mantle tissue usually exceeded that in the digestive gland, particularly during 1988. By excising these two tissues, >90 per cent of the total toxicity could be eliminated. Relative and absolute amounts of PSP toxins among various tissues are in a state of flux; in addition to metabolic conversions, toxins are subject to mobilization and transfer among tissue compartments. For example, PSP toxins accumulated in the digestive gland of the Japanese scallop *Patinopecten yessoensis* may shift to the mantle before being secreted or leaked into the surrounding seawater (Inoguchi et al. 1990).

PSP toxin levels in gonadal tissue are usually below the regulatory limit for human consumption accepted in North America and many other countries (80 µg STXeq/100g); most samples are below the detection limit of the AOAC mouse bioassay (30-42 µg STXeq/100g). As would be expected from the fact that part of the scallop intestine passes through the gonadal tissue (Bourne 1965), highest PSP toxicity in gonads occurs when toxin levels in the digestive gland are also maximal. In rare cases, PSP toxin levels substantially in excess of the regulatory limit have been found in gonads (Microbiology Division, Dept of Health and Welfare, Canada, Black's Harbour, New Brunswick, Canada, unpublished; Cembella and Shumway 1991). Nevertheless, attempts to directly correlate PSP toxicity in gonads with levels in other tissues or with total body toxin burden have not been successful (Watson-Wright et al. 1989, Cembella and Shumway, unpublished data).

Adductor muscles always contain less PSP toxin than the corresponding viscera, even when toxin levels are extremely high in other tissues. In fact, scallop adductor muscles are usually free of detectable PSP toxins (Medcof et al. 1947, Bourne 1965, Watson-Wright et al. 1989, Shumway 1990, Gillis et al. 1991), although in exceptional circumstances levels exceeding the regulatory limit have been found (Noguchi et al. 1984). A few samples from the Gulf of Maine, collected during the summers of 1988 and 1989, contained detectable PSP toxin (mostly GTX1+4 and GTX2+3) as determined by HPLC-FD, but toxin levels were never above the regulatory limit. Relative weight-specific toxicity did not exceed 1 per cent of the total toxicity among all tissues (Figure 2). No reliable estimates of PSP toxicity in adductor muscles can be made by extrapolation from the toxicity of surrounding viscera (Beitler 1991, Watson-Wright et al. 1989, Cembella and Shumway, unpublished data).

Figure 2

Seasonal variation in relative weight-specific PSP toxicity (% total) found in various tissue compartments, and relative toxin composition (% molar) found in scallops from offshore (80m depth) and inshore (20m depth) stations in the Gulf of Maine 1988-89



Analysis of PSP toxin profiles from Gulf of Maine scallops supported previous findings (Fix-Wichmann et al. 1981, Shimizu and Yoshioka 1981) that the toxin composition may differ considerably from that of the dinoflagellate (*Alexandrium* spp.) responsible for the toxicity. Maximal PSP toxicity in scallops is not usually synchronous with peak cell densities of toxic dinoflagellates (Kodama and Ogata 1988); a significant lag phase between the appearance of the bloom and maximum body burden of toxin is typically observed. A substantial shift in the toxin profile from the less potent N-sulfocarbamoyl toxins (e.g. C1 and C2), which often dominate in the dinoflagellate, to higher toxicity carbamate derivatives (e.g. GTXs, NEO, and STX) may occur as a result of metabolic conversions and physico-chemical processes in the scallop digestive system.

In controlled detoxification experiments with *Patinopecten yessoensis* (Oshima 1991) and *Pecten maximus* (Lassus et al. 1989), both the anatomical distribution and toxin profile among different tissues were shown to change over time. Specifically, in *Pecten maximus*, a progressive decrease in GTX3, C1 and C2 was accompanied by an increase in GTX2 during the latter stages of detoxification; in *Patinopecten yessoensis*, as GTX1+4 decreased, GTX2+3 increased in mantle tissues, whereas in the kidney, GTX1+4 decreased with a corresponding increase in NEO and STX. Such putative bioconversions are consistent with the loss of the N-sulfocarbamoyl group, the epimerization of GTX2+3, the reduction of the N-1 hydroxyl moiety, and the loss of the hydroxysulfate group at C-11 (Figure 1). Biotransformation of toxins within scallop tissues from less toxic sulfocarbamoyl derivatives to carbamate analogues may also account for some increase in toxicity observed over time in *P. magellanicus* (Hsu et al. 1979, Shimizu and Yoshioka 1981).

Substantial differences in the relative amounts of PSP toxins (per cent molar) in scallops from the Gulf of Maine were more evident, among various tissue compartments, than were seasonal variations and geographical differences between populations (Figure 2). The toxin composition of digestive glands and mantles tended to be similar and was dominated by C1+C2 and GTX2+3. The PSP toxin profile of gill tissue was extremely erratic, but often contained a substantial proportion of GTX1+4. In the gills, toxins C1 and C2 were clearly dominant in the inshore population during both 1988 and 1989; however, this was not the case for the offshore stocks. The PSP toxin profile in gonads (when toxin was present) was dominated by C1, C2 and GTX2+3, with a relative decline in C1+C2 and NEO, and a concomitant increase in GTX2+3 and GTX1+4, appearing towards the end of the summer of 1988 for the offshore population. This is the clearest evidence for biotransformation within any of the tissues. Saxitoxin (STX) was a significant toxin component in digestive gland, mantle and gill tissue, but was much rarer in gonads and adductor muscles. There was no apparent systematic seasonal trend in the proportions of carbamate to N-sulfocarbamoyl toxins among the various tissues.

Genetic manipulations and substantial equivalence

Genetic techniques applied to the enhancement of shellfish stocks may be generally subdivided into cytogenetic and molecular methods (reviewed by Allen, 1987). Most current efforts in aquatic biotechnology to manipulate shellfish genetically (beyond conventional selective breeding) involve the induction of polyploidy – typically the triploid state. The insertion of foreign genetic material into the shellfish genome (transgenic induction) and advanced recombinant DNA technology remain at a preliminary stage, and these techniques are not yet applied to scallops on a commercial scale. The theoretical benefits to aquaculture of such biotechnological manipulations include the potential for: i) increased growth rate; ii) enhanced disease and parasite resistance; iii) temporal control of the reproductive cycle; and iv) decreased juvenile mortality. The downside

risk – the possible escape and interbreeding of genetically engineered stocks with wild populations, with deleterious effects – is an important consideration (Maclean and Penman 1990) but is not technically a food safety issue.

The induction of triploidy, a technique successfully pioneered and developed with the American oyster *Crassostrea virginica* (Allen 1987), has been achieved with the bay scallop *Argopecten* (Tabarini 1984); however, the net benefits to commercial aquaculture remain equivocal. Ostensibly, the retardation of gonad production should result in enhanced somatic growth and the maintenance of tissue quality throughout the reproductive cycle. An important question regarding shellfish contamination by marine phycotoxins is the degree to which toxin accumulation and biotransformation kinetics determined for natural populations can be extrapolated to genetically modified aquaculture stocks. As a corollary, do food safety regulations and appropriate analytical methodologies for toxicity determination require modification, or does the concept of "substantial equivalence" apply? At present, any such judgements are largely inductive, since definitive case studies comparing the disposition of biotoxins in natural populations versus their genetically engineered counterparts employed in aquaculture systems are non-existent. In any case, triploid stocks are not markedly genetically divergent from the wild type, and appear to pose little threat to the substantial equivalence concept. Since PSP toxins are acquired by shellfish from exogenous environmental sources, rather than through endogenous biosynthesis, there is no *a priori* reason why genetic modification would have a dramatic qualitative affect on the metabolism and elimination of such toxins. It is conceivable that changes in growth rate, basal metabolism (including glycogen storage), reproductive physiology and gonadal mass resulting from chromosomal manipulations and/or recombinant DNA technology may affect indirectly the kinetics of toxin catabolism and elimination, and perhaps tissue partitioning of toxin components. Unknown pleiotropic effects of genetic manipulations might also alter the synthesis and activity of enzymes responsible for PSP toxin biotransformation, particularly in the digestive tract. However, it is unlikely that such changes would be of sufficient magnitude to warrant substantial modification of PSP toxin monitoring strategies or analytical techniques for toxins.

Conclusions

- Establishment of food safety guidelines with particular emphasis on phycotoxin levels in individual tissues is necessary if scallops are to be marketed whole or in conjunction with tissues other than adductor muscles.

- Scallop aquaculturists and regulatory authorities should be acutely aware of the potential risks associated with phycotoxins and the consequences to human health of marketing various scallop products exposed to toxic algae.

- Safe marketing of whole or "roe-on" scallops is a high risk proposition, both economically and in terms of human health implications, given the long toxin retention times and high PSP toxicity levels often found in scallops.

- With respect to the accumulation of exogenous marine biotoxins (specifically, PSP toxins in scallops), it is reasonable to apply the substantial equivalence concept developed from wild populations to analogous genetically engineered aquaculture stocks.

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