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1 **Interaction between norovirus and Histo-Blood Group Antigens: a key to**
2 **understanding virus transmission and inactivation through treatments?**

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15 ¹ Abbreviations

16 **Abstract**

17 Human noroviruses (HuNoVs) are a main cause of acute gastroenteritis worldwide. They are
18 frequently involved in foodborne and waterborne outbreaks. Environmental transmission of the virus
19 depends on two main factors: the ability of viral particles to remain infectious and their adhesion
20 capacity onto different surfaces. Until recently, adhesion of viral particles to food matrices was mainly
21 investigated by considering non-specific interactions (e.g. electrostatic, hydrophobic) and there was
22 only limited information about infectious HuNoVs because of the absence of a reliable *in vitro*

1

BP: Binding pocket; CaCV: Canine calicivirus; Ct: Concentration of chlorine x Time given in mg.min.L⁻¹; ELISA: Enzyme-linked immunosorbent assay; FCV: Feline calicivirus; FUT: Fucosyltransferase; GI: Genogroup I; GII: Genogroup II; HAV: Hepatitis A virus; HBGAs: Histo-Blood Group Antigens; HID₅₀: 50% human infectious dose; HIE: Human intestinal enteroids; HPP: High pressure processing; HuNoV: Human norovirus; ISO: International Organization for Standardization; MNV: Murine norovirus; ORFs: Open reading frames; PCR: Polymerase chain reaction; PFU: Plaque-forming unit; PGM: Porcine gastric mucin; PV: Poliovirus; RT-qPCR: Reverse-transcription quantitative PCR; RV: Rotavirus; TCID₅₀: 50% tissue culture infective dose; TEM: Transmission electron microscopy; TFL: Time to reduce the first log₁₀; TV: Tulane virus; UV: Ultraviolet; VLPs: Virus-like particles; WWTPs: Wastewater treatment plants.

23 HuNoV cultivation system. Many HuNoV strains have now been described as having specific binding
24 interactions with human Histo-Blood Group Antigens (HBGAs) and non-HBGA ligands found in food
25 and the environment. Relevant approaches to the *in vitro* replication of HuNoVs were also proposed
26 recently. On the basis of the available literature data, this review discusses the opportunities to use this
27 new knowledge to obtain a better understanding of HuNoV transmission to human populations and
28 better evaluate the hazard posed by HuNoVs in foodstuffs and the environment.

29

30 Keywords: Norovirus; Histo-Blood Group Antigens; Infectivity; Foods; Virus transmission.

31

32 **1. Introduction**

33 Poliovirus (PV), discovered at the beginning of the 20th century, was the first enteric virus to be
34 described that is transmitted through food and water. Cell culture of PV, as proposed by Enders and
35 Wellers in 1949, allowed the development of the first vaccination strategies, the evaluation of the viral
36 contamination of food and water, and the optimization of processing technologies to inactivate
37 infectious particles. PV risk is currently under control worldwide. Some basic and applied
38 improvements are currently required to manage other enteric viruses, especially human noroviruses
39 (HuNoVs).

40 HuNoVs are a leading worldwide cause of acute gastroenteritis, of which more than 200,000 cases are
41 reported annually (Kirk et al., 2015). HuNoVs are the most prevalent pathogens associated with
42 foodborne or waterborne outbreaks reported in the USA (CDC 2018), and have been ranked in the top
43 three in Europe for many years (EFSA, 2017). HuNoVs were discovered in 1972 (Kapikian et al.,
44 1972), and the first reliable approaches to the *in vitro* replication of HuNoVs, using human intestinal
45 enteroids (HIE) or zebrafish larvae, were recently published (Ettayebi et al., 2016; Todd and Tripp,
46 2020; Van Dycke et al., 2019). As with PV, these first approaches to the replication of HuNoVs are
47 still highly complex and time-consuming, but are facilitating research intended to improve our
48 understanding of virus-host interactions and of strategies for the mitigation of HuNoV transmission
49 (Atmar et al., 2018).

50 The routine application of polymerase chain reaction (PCR) methods at the end of the 20th century
51 supported improved epidemiological studies, greater understanding of the genetic evolution of HuNoV
52 strains, and the development of diagnostic assays in humans (Ambert-Balay et al., 2005; Atmar et al.,
53 2018; Beek et al., 2018; Bull et al., 2010; Gallimore et al., 2007). Because of the absence of a reliable
54 *in vitro* HuNoV cultivation system that could be routinely used, quantitative reverse transcription PCR
55 (RT-qPCR) approaches using a standard method (ISO 15216-1, 2017) were thought to be useful for
56 the management of the risk of HuNoV in foodstuffs. However, the usefulness of this ISO standard for
57 surveillance in vulnerable foodstuffs and water has limitations due to its inability to discriminate
58 infectious from non-infectious HuNoVs once a viral genome has been detected. It has been widely
59 demonstrated that viral genomes persist for longer in the environment than infectious particles
60 (Gassilloud et al., 2003; Hartard et al., 2015).

61 In this context, there is an urgent need to develop more reliable methods of estimating HuNoV
62 infectivity in food and the environment and to better evaluate the efficacy of processing technologies
63 that could be used by the food and water industries. Many strategies have been developed over the past
64 two decades. The use of culturable viruses (e.g. feline calicivirus (FCV), murine norovirus (MNV),
65 Tulane virus (TV), or fecal coliphages) or virus-like particles (VLPs) as HuNoV surrogates has
66 frequently been proposed, but their capacity to mimic the behavior of infectious HuNoVs has not been
67 clearly demonstrated (Ausar et al., 2006; Bosch et al., 2018; Boudaud et al., 2012; Hirneisen et al.,
68 2010; Manuel et al., 2018; Sato et al., 2016; US EPA, 2006; WHO, 2011). Molecular-based methods
69 (e.g. detection of the whole genome, the use of enzymatic pre-treatments or intercalating dyes prior to
70 genome detection, and detection of oxidative damages to the capsid) are regularly developed to
71 evaluate the integrity of the genome and/or the viral capsid, but they have not been fully adapted for
72 use (Kostela et al., 2008; Manuel et al., 2018; Nuanualsuwan and Cliver, 2002; Oristo et al., 2018;
73 Sano et al., 2010).

74 The use of Histo-Blood Group Antigens (HBGAs) is another approach proposed for estimating the
75 integrity of the HuNoV capsid (Li et al., 2012b; Lou et al., 2012; Manuel et al., 2018; Moore and
76 Jaykus, 2017). HBGAs are complex carbohydrates linked to glycolipids or glycoproteins, found on red
77 blood cells and mucosal epithelial cells, or present as free antigens in biological fluids, such as saliva

78 (Huang et al., 2005). They have been described as putative attachment factors for several HuNoV
79 strains and promote the infection of host cells (Ettayebi et al., 2016; Harrington et al., 2002; Hutson et
80 al., 2002; Lindesmith et al., 2003; Marionneau et al., 2002; Rockx et al., 2005). A specific type of
81 carbohydrate, called HBGA-like carbohydrates, which have the capacity to bind to HuNoVs, was also
82 recently identified in certain vulnerable food products (e.g. lettuce, oysters) (Almand et al., 2017a).
83 Advances in knowledge of the structure of HuNoV and HBGA-binding to HuNoVs have already been
84 well described (Atmar et al., 2018; Shirato, 2011; Tan and Jiang, 2014, 2005). This review will
85 therefore mainly focus on the ability of HBGA-binding to be used to i) select only infectious particles
86 prior to genome detection and, ii) participate in the environmental transmission of HuNoV. To do this,
87 this review will consider the recent knowledge on the presence of HBGA-like carbohydrates in
88 vulnerable foodstuffs. On the basis of the literature data, we compare the virus removal rates during
89 processing technologies between infectious HuNoV surrogates, determined by cell culture; HuNoV
90 genome, directly quantified by RT-qPCR; and HuNoV genome, after HBGA-binding assays. We then
91 attempt to determine whether HuNoV interactions with the HBGA-like carbohydrates present in
92 specific food items could influence the transmission of some HuNoV genotypes.

93

94 **2. Human Norovirus**

95 HuNoVs belong to the family *Caliciviridae* and the genus *Norovirus*. They are non-enveloped viruses
96 (~40 nm in diameter) with an icosahedrally symmetrical capsid, and positive-sense single-stranded
97 RNA (~7,500 nucleotides), containing three open reading frames (ORFs). ORF1 encodes non-
98 structural proteins, while ORF2 and ORF3 encode for the major (VP1, 530 amino acids) and minor
99 (VP2, 212 amino acids) capsid proteins, respectively. The capsid is composed of 180 copies of VP1
100 assembled into 90 dimers and a few copies of VP2. VP1 is organized into two domains, the shell
101 domain (S) and the protruding domain (P) which is subdivided into P1 and P2 subdomains (Donaldson
102 et al., 2010). P2 subdomain, which contains the putative receptor-binding sites, is highly variable and
103 is located on the external surface of the capsid (**Fig. 1**). Thus, P2 subdomain has direct interactions

104 with the local environment (Cao et al., 2007; Chen et al., 2011; Hansman et al., 2011; Shanker et al.,
105 2011).

106 HuNoVs, mainly belonging to genogroup I (GI) and genogroup II (GII), are subdivided into at least 9
107 (GI.1–9) and 25 (GII.1–27) genotypes, respectively (Nordgren and Svensson, 2019). A recent study
108 highlighted structural polymorphism and different particle sizes between and within HuNoV
109 genogroups (Jung et al., 2019). GII.4 HuNoV is the most prevalent genotype, responsible for about
110 70% of total HuNoV outbreaks reported annually (Beek et al., 2018). HuNoVs exhibit high genetic
111 and antigenic variabilities, as shown by the emergence of the last six pandemic strains since 1995
112 (Beek et al., 2013; Bull et al., 2010; Eden et al., 2014, 2010; Lopman et al., 2004; Vinjé et al., 1997;
113 Yen et al., 2011). On the basis of the analysis of the amino acid sequence of VP1 in 164 HuNoV
114 strains, Zheng et al. (2006) showed different levels of variability within the same species (e.g. 0–
115 14.1% for Norwalk virus), the same genotype (e.g. 14.3–43.8% for GI.1 HuNoVs), and the same
116 genogroup (e.g. 44.9–61.4% for GI HuNoVs). The evolution of the VP1 protein influences resistance
117 to human infection because single amino acid changes in or peripheral to receptor-binding domains
118 may i) change receptor-binding specificities (Rougemont et al., 2011) and/or ii) promote escape from
119 the immune response (Donaldson et al., 2010). A complete overview of the antigenic variability of
120 HuNoVs has been well described (White, 2014).

121 Human infection by HuNoVs can be diagnosed in clinical samples through the detection of i) VP1
122 proteins, using enzyme-linked immunosorbent assay (ELISA) approaches; ii) viral genomes, using
123 RT-qPCR; or iii) whole virus particles, using transmission electron microscopy (TEM) (Rabenau et
124 al., 2003). Although a correlation could be made between HuNoV genome detection and infectious
125 particles from symptomatic individuals, these approaches have not yet proven sufficient to detect
126 infectious HuNoVs in food and environmental matrices. In humans, the 50% human infectious dose
127 (HID₅₀) of Norwalk virus (GI.1) has been estimated to have between 18 and 2,800 genomic
128 equivalents, by considering the viral aggregation (Atmar et al., 2014; Teunis et al., 2008). This HID₅₀
129 needs to be better defined, using more accurate methods, because the ratio of genomes to infectious
130 particles may change over time or during disinfection treatments, thus making it impossible to link the
131 number of genome copies to HID₅₀ in food or the environment. Like culturable pathogenic enteric

132 viruses such as poliovirus 1 (PV1) or rotavirus (RV), the HID_{50} ranges from 1 to 100 infectious
133 particles, detected using the 50% tissue culture infective dose ($TCID_{50}$) or plaque-forming unit (PFU)
134 methods (Minor et al., 1981; Ward et al., 1986). As with other enteric viruses, the HID_{50} estimated for
135 norovirus seems to be low: from 1 to 100 infectious particles (Yezli and Otter, 2011).
136 Recent advances in HuNoV replication models, such as HIE (Ettayebi et al., 2016) and zebrafish
137 larvae (Van Dycke et al., 2019), will probably lead to the development of a reliable method in the
138 future, allowing a better estimation of the HID_{50} of HuNoVs and the detection of infectious HuNoVs in
139 food, but significant improvements are still needed in terms of sensitivity, specificity, and accuracy.

140

141 **3. HBGA-binding to HuNoVs**

142 Numerous studies have described about HBGA-binding to HuNoVs. HBGAs are complex
143 carbohydrates resulting from the sequential addition of different monosaccharide units to precursor
144 structures present on cell surfaces. The biosynthesis of ABH and Lewis HBGAs (i.e. Le^a , Le^x , Le^b ,
145 Le^y , S Le^x , A, B, or H antigens) is governed by the ABO and fucosyl-transferase *FUT2* and *FUT3* gene
146 families. The expression of active or non-active *FUT2* defines secretor or non-secretor status,
147 respectively. This has been widely described in the literature (de Graaf et al., 2016; Marionneau et al.,
148 2002, 2001; Tan and Jiang, 2014). The phenomenon of HBGA-binding to HuNoVs through the
149 “binding pocket” (BP), which is located in a region of the P2 subdomain of VP1 has also been
150 extensively reviewed (Donaldson et al., 2008; Ruvoën-Clouet et al., 2013; Shirato, 2011; Tan and
151 Jiang, 2014, 2010). Polymorphic HBGA expression and the natural evolution of HuNoVs contribute to
152 the diversity of HBGA-binding patterns (Shirato et al., 2008; Tan et al., 2009). Interactions between
153 HuNoVs and HBGAs can be classified according to their relative affinities. Three distinct groups have
154 been proposed by Huang et al (2005), independent of HuNoV genogroup and genotype: the “A/B
155 binding group,” the “Lewis binding group,” and the “no binding group.”

156 Numerous *in vitro* and *in vivo* studies have shown the importance of HBGAs in HuNoV infection. The
157 role of HBGA-binding during the process of host cell infection needs to be clarified. Current
158 knowledge suggests two possibilities: i) HBGAs may act as a cellular receptor (or co-receptor), which
159 participates in the release of the HuNoV genome into the host cell; or ii) HBGA-binding may facilitate

160 its passage through the gastrointestinal tract up to the host cell. Many studies have provided evidence
161 that human susceptibility to HuNoV infection is dependent on both polymorphic HBGA expression
162 and HuNoV genotype (Hutson et al., 2002; Lindesmith et al., 2003; Nordgren and Svensson, 2019;
163 Rockx et al., 2005; Tan and Jiang, 2014). It is widely acknowledged that non-secretor individuals are
164 less susceptible to HuNoV infection than secretor individuals because most HuNoVs recognize ABO
165 secretor antigens (Tan and Jiang, 2014). Conversely, other studies observed no correlation between
166 HuNoV infection and ABO or secretor status (Ayouni et al., 2015; Larsson et al., 2006; Lindesmith et
167 al., 2005; Sharma et al., 2019). Recently, host cell infection by HuNoVs using HIE demonstrated that
168 the replication of GII.4 — but not GII.3 — strains is dependent on secretor status (Ettayebi et al.,
169 2016). As described below, some HuNoV strains do not recognize any HBGA type (Huang et al.,
170 2005), which reinforces the assumption that human susceptibility is mainly dependent on HuNoV
171 genotype.

172 In any case, it has never been demonstrated that HBGA-binding to the BP allows genome entry into
173 the host cell. It can therefore be concluded that the presence of HBGAs is not an exclusive
174 requirement for HuNoV replication.

175 HBGAs or HBGA-like carbohydrates present on bacteria found in the human gut and their interactions
176 with HuNoVs have been well described (Almand et al., 2019, 2017a, 2017b). Various mechanisms
177 that may promote or prevent HuNoV infection in humans have been well highlighted by Monedero et
178 al. (2018). One study evidenced that the gut bacterium *Enterobacter cloacae* bound HuNoVs through
179 the H-like carbohydrate present on the bacterial surface (Miura et al., 2013). The role of *E. cloacae* for
180 HuNoV replication needs to be clarified, since discrepancies have been reported between *in vivo* and
181 *in vitro* studies (Jones et al., 2014; Lei et al., 2016). The ability of HuNoVs to bind to lactic acid
182 bacteria present in the human microbiota through HBGA-like substances, has also been demonstrated
183 (Rubio-del-Campo et al., 2014). The same authors made the assumption that surface carbohydrates on
184 bacteria are responsible for HuNoV attachment.

185 Other factors found in the human gastrointestinal tract may also promote HBGA-binding to HuNoVs.
186 It has been shown that bile enhanced the replication of HuNoV strains in HIE (Ettayebi et al., 2016),
187 which is explained by a stabilization of the P domain that allows for better interaction with the fucose

188 residue (Kilic et al., 2018). Trypsin could also promote HBGA-binding to HuNoVs (Huo et al., 2017,
189 2016). Current data from the literature suggests that HBGA-binding to HuNoVs is specific and highly
190 diverse. HBGAs are currently considered to be putative attachment factors for several HuNoV strains
191 that promote human infection. HuNoV replication in the host cell could be enhanced by other factors,
192 such as bacterial microbiota, bile, or proteases, but some progress will be needed to improve our basic
193 knowledge. However, it remains unclear to what extent HuNoV–HBGA interaction influences the
194 infectivity of HuNoVs.

195

196 **4. Interaction with HBGAs: proof of infectivity?**

197 There is currently an urgent need to improve the management of HuNoV hazard in food and the
198 environment. When considering the behavior of viruses outside the host cell, two main factors have to
199 be taken into account: inactivation and adhesion capacity. With regard to inactivation: it is well known
200 that infectious particles may be exposed to various inactivation factors in the environment or during
201 food processing and water treatment and that these factors affect the integrity of viral particles but not
202 the detection of the target viral genome and/or antigen. Therefore, characterization of virus infectivity
203 is critical for better evaluation of HuNoV hazard in foodstuffs and the efficacy of the processing
204 technologies used in the food and water industries.

205 There is already a lot of available data on the effects of inactivation factors (e.g. temperature,
206 sanitizers, ultraviolet (UV) light, high pressure processing (HPP)) on several culturable viruses (e.g.
207 PV, FCV, Hepatitis A virus (HAV), MNV, TV, F-specific RNA phages, adenovirus) in different
208 matrices (e.g. drinking water, wastewater, groundwater, oysters, berries, fresh vegetables). It is well
209 known that viral genomes are more resistant to inactivation factors in the environment or processing
210 technologies than infectious viruses. This has led to an overestimation of the HuNoV hazard in
211 vulnerable foodstuffs, but also an underestimation of the virucidal impact of food processing and
212 water treatments (Espinosa et al., 2008; Ogorzaly et al., 2010; Simonet and Gantzer, 2006b). The
213 impact of different processing technologies on the reduction of HuNoV genomes and the discrepancy
214 between the inactivation of infectious culturable HuNoV surrogates and the reduction of the
215 corresponding viral genomes have been well reviewed (Bosch et al., 2018; DiCaprio et al., 2013;

216 Hirneisen et al., 2010; Knight et al., 2016; J. Li et al., 2012). Clinical trials have provided few data on
217 the survival of infectious HuNoVs in groundwater at room temperature or after disinfection treatment
218 (i.e. HPP) (Leon et al., 2011; Seitz et al., 2011).

219 Demonstration of cytopathic effects on host cell cultures is the most reliable method for the detection
220 of infectious viruses. As described above, the *in vitro* replication of HuNoVs is now possible using
221 HIE or zebrafish larvae (Ettayebi et al., 2016; Van Dycke et al., 2019). These approaches will
222 undoubtedly improve knowledge (e.g. cellular biology, survival in the environment, and the validation
223 of HuNoV indicators, for example), but they will probably not be suitable for routine food testing or
224 for the assessment of disinfection treatments, owing to their complexity, high cost, low sensitivity, and
225 time-consuming nature. In addition, extraction and concentration procedures for infectious viruses in
226 foodstuffs are matrix dependent and yield variable recovery rates.

227 The detection and quantification of HuNoV genomes in food are currently performed using ISO
228 15216-2 (2019) and ISO 15216-1 (2017) standard methods, respectively. The prevalence of HuNoV
229 genomes in commercial food products ranged from 9.0% and 71.6% for oysters, 6.7% and 16.0% for
230 berries, and 5.0% and 28.2% for lettuce (Baert et al., 2011; EFSA, 2018; Loutreul et al., 2014;
231 Lowther et al., 2012; Pérez-Rodríguez et al., 2014; Schaeffer et al., 2013). A recent analysis of the
232 European baseline survey of HuNoVs in oysters showed that the prevalence of HuNoV genomes was
233 estimated at 34.5% and 10.8% in European production areas and dispatch centers, respectively (EFSA,
234 2019).

235 Based on these prevalence data, new approaches are required for the specific detection of infectious
236 HuNoVs in vulnerable foodstuffs and the environment. Measurements of the capsid integrity of
237 HuNoVs, using HBGA-binding assays prior to genome detection, could be relevant. The benefits and
238 drawbacks of this approach to predicting HuNoV infectivity have been comprehensively reviewed by
239 Manuel et al. (2018). Some authors have suggested that HBGA-binding assays could indicate the
240 extent of capsid damage in response to inactivation factors, and allow to better estimate HuNoV
241 hazard in vulnerable foodstuffs, by discriminating infectious from non-infectious particles (Afolayan
242 et al., 2016; Dancho et al., 2012; Moore et al., 2017). However, another study highlighted the fact that

243 HuNoVs may specifically bind to HBGAs for particles with i) intact capsid with altered genome or, ii)
244 intact genome with capsid damage(s) located in surrounding regions of the BP (Robin et al., 2019).
245 To more clearly define the potential relevance of HBGA-binding assays to the selection of infectious
246 HuNoVs, this review has collected literature data related to the inactivation of culturable HuNoV
247 surrogates (i.e. MNV, FCV, canine calicivirus (CaCV), TV, HAV, and PV) and data related to the
248 reduction in HuNoV genomes after four processing technologies (heat, chlorine, HPP, UV light).
249 MNV, FCV, CaCV, and TV were selected because they belong to the *Caliciviridae* family. HAV and
250 PV, belonging to the *Picornaviridae* family, were selected because of their high resistance to
251 inactivation treatments, such as heat and UV light (Bertrand et al., 2012; Park et al., 2015). The use of
252 these diverse surrogates gives us a better overview of how the behavior of HuNoVs is affected by
253 different processing technologies. Data on reduction of HuNoV genomes were obtained from direct
254 detection of viral genomes using RT-qPCR and from HBGA-binding assays, followed by genome
255 detection (**Table 1**). Studies using porcine gastric mucin (PGM) before genome detection to evaluate
256 the capsid integrity of HuNoVs after different treatments were also included because PGM (which
257 contains A-like and Lewis-like HBGAs, and sialic acids) can bind to some GI and GII HuNoV strains
258 (Tian et al., 2007b). All these data have been compared to determine whether HBGA-binding to
259 HuNoVs followed by genome detection can be a reliable way of discriminating infectious from non-
260 infectious particles.

261

262 **4.1. Heat treatment**

263 The inactivation of infectious HuNoV surrogates and reduction of HuNoV genomes have been
264 examined in various foodstuffs and water, at different temperatures and with different exposure times.
265 Bertrand et al. (2012) thoroughly reviewed the impact of heat treatment on virus inactivation in simple
266 and complex matrices and described a specific regression model to determine the time (in days) to
267 reduce the first log₁₀ (TFL) as a function of temperature according to various parameters (virus
268 species, detection method, matrix, low/high temperature). According to that review, the regression
269 model was used to obtain the TFL values of infectious HuNoV surrogates (i.e. HAV, MNV, CaCV,
270 and FCV) as a function of temperature, for temperatures ranging from 50°C to 80°C, in simple

271 matrices (i.e. synthetic media, drinking water, groundwater). A second regression model was drawn up
272 for HuNoV genomes in simple matrices, based on the TFL values used in that review and those
273 determined by another, more recent studies (Bertrand et al., 2012; Escudero-Abarca et al., 2014). Both
274 regression models of infectious HuNoV surrogates and HuNoV genomes directly quantified by RT-
275 qPCR were compared to the TFL values of HuNoV genomes quantified after HBGA-binding assays
276 calculated from data obtained by Robin et al. (2019) and Wang and Tian (2014) (**Fig. 2**).

277 As extensively described in the literature, heat-induced inactivation of infectious HuNoV surrogates is
278 known to increase with temperature (Bertrand et al., 2012). Conversely, the decay in TFL values of
279 HuNoV genomes is systematically lower than that of the infectious HuNoV surrogates in the 50–80°C
280 temperature range. This observation confirms the greater persistence of viral genome compared to
281 infectious particles, thus reinforcing the proof that viral genome detection alone cannot predict the
282 behavior of infectious particles after heating. However, quantifying HuNoV genomes after HBGA-
283 binding assays reduces the overestimation of potential infectious HuNoVs provided by the direct
284 detection of viral genome. This overestimation was higher than 1.8 log₁₀ for temperatures below 65°C
285 and remained below 1.0 log₁₀ at 72°C. For infectious HuNoV surrogates, 20.6 and 1.3 additional
286 minutes were required to reach a 1.0 log₁₀ reduction in HuNoV genomes after HBGA-binding assays
287 at 65°C and 72°C, respectively. RNase treatments before genome detection by RTqPCR were often
288 used for assessing capsid integrity (i.e. viral particles with damaged capsid allows entry of RNase and
289 genomes of such particles are no more detected by RT-qPCR). Similar results were reported by
290 Walker et al. (2019) when the assessment of the capsid integrity of GA bacteriophages, assessed using
291 two different approaches (i.e. RNase and PGM assays prior to genome detection), was compared with
292 the corresponding number of infectious particles after heating. Neither method provided log₁₀
293 reductions similar to those obtained from cultures of infectious GA bacteriophages at temperatures
294 below 72°C held for 5 minutes.

295 It is widely acknowledged that heat treatments mainly cause damages to capsid integrity, rather than to
296 the RNA genome. For GII.4 HuNoVs, the critical temperature leading to capsid disruption seems to be
297 close to 70°C (Robin et al., 2019). At temperatures below 60°C, mechanisms of virus inactivation

298 seem to be mainly due to minor modifications/alterations of the capsid, since the viral genome was not
299 accessible to RNAses (Brié et al., 2016).

300 In conclusion: HBGA-binding assays, followed by HuNoV genome detection can reduce
301 underestimation of the virucidal efficacy of heat treatments that induce significant changes to the
302 capsid structure (i.e. above 70°C). However, this approach does not prevent an overestimation of
303 infectious HuNoVs following heat treatments ranging from 50°C to 70°C because of the minor
304 changes of the capsid.

305

306 **4.2. Chlorine treatment**

307 Chlorinated water is widely used in many countries for washing fresh vegetables (e.g. salads, carrots)
308 or berries (e.g. raspberries). Chlorine disinfection is also widely used in drinking water plants prior to
309 distribution. The virucidal efficacy of chlorine disinfection has been evaluated in many studies over
310 the years (Bosch et al., 2018; Knight et al., 2016). $\log_{10} C/C_0$ values of infectious HuNoV surrogates
311 (i.e. MNV, TV, and FCV) and HuNoV genomes (whether or not they are associated with HBGA-
312 binding assays) as a function of chlorine doses in water or cell culture media were collected from the
313 literature data. The results are shown in **Fig. 3**. C_0 corresponds to the value obtained at time 0 and C
314 corresponds to the value obtained after chlorine disinfection for a given Ct value. Ct values were
315 defined as the free chlorine concentration (mg.L^{-1}) multiplied by the contact time (in minutes).

316 As expected, chlorine-induced inactivation of infectious HuNoV surrogates increases with Ct value.
317 More than 4.0- \log_{10} inactivation was obtained for Ct values from 2.5 mg.min.L^{-1} for MNV. Reductions
318 in HuNoV genomes directly quantified by RT-qPCR as a function of Ct values were highly variable.
319 The efficacy of chlorine disinfection on HuNoV genomes seems to be dependent on study design, and
320 particularly on the methods used to measure free chlorine during the experiments and the purification
321 of HuNoV particles before treatment. “Purified HuNoVs” from human stool samples were more
322 sensitive to chlorine disinfection than “untreated HuNoVs” for the same Ct value. For example, a 3.6
323 \log_{10} reduction in genomes of “purified HuNoVs” was obtained for a Ct value of 15 mg.min.L^{-1} , while
324 a 0.4 \log_{10} reduction in genomes of “untreated HuNoVs” was reached for a Ct value of 250 mg.min.L^{-1}
325 (Kitajima et al., 2010; Tung et al., 2013). The matrix effect promotes the persistence of HuNoVs

326 during chlorine disinfection. The efficacy of decontamination depends on the amount of organic
327 matter present in water, since this promotes the formation of chlorination by-products, but also the
328 accessibility of viral particles to free chlorine (Bosch et al., 2018). As observed, after heating, HBGA-
329 binding assays followed by HuNoV genome detection reduce the underestimation of the virucidal
330 efficacy of chlorine disinfection provided by direct HuNoV genome detection. Free chlorine exerted a
331 dose-dependent reduction in HuNoV genomes after HBGA-binding, as demonstrated by Wang and
332 Tian (2014).

333 The mechanisms of virus inactivation induced by free chlorine have been shown to damage both the
334 capsid and the genome (Brié et al., 2017; Wigginton et al., 2012b). Some authors showed that some
335 particles may no longer recognize their receptors, while others are no longer able to inject their
336 genomes into the host cell (Wigginton et al., 2012b). Both capsid disruption and RNA damages were
337 observed by the same authors, even though the capsid structures of the viruses remained unbroken
338 after high doses of chlorine (Brié et al., 2017; Loison et al., 2016). Another study showed a positive
339 correlation between the reduction in infectious human astrovirus and the amount of oxidative damage
340 to the viral capsid (i.e. carbonyl groups) after chlorine disinfection (Sano et al., 2010). The same
341 authors suggest that the detection of carbonyl groups could be useful to estimate the reduction in
342 HuNoV infectivity induced by oxidative treatments. Using Q β and MS2 bacteriophages, Bastin et al.
343 (2020) have located oxidative damages to viral particles, and especially to cysteine, methionine,
344 tyrosine, and tryptophan.

345 In conclusion: the reduction in the underestimation of HuNoV inactivation induced by chlorine
346 disinfection using HBGA-binding assays prior to genome detection can be explained either by capsid
347 disruption or by oxidative damages in the BP region. However, this approach has the drawback that it
348 is unable to specifically select infectious HuNoVs, since oxidative damages can be incurred in the
349 viral genome and/or capsid amino acids located in remote regions of the BP.

350

351 **4.3. High pressure processing**

352 For the past two decades, use of HPP has been a promising alternative for food products that cannot be
353 treated using heat or chlorine disinfection. HPP compresses food suspended in liquid and then rapidly

354 releases the pressure (Barbosa-Cánovas et al., 1998). The virucidal impact of HPP on contaminated
355 foodstuffs has been thoroughly reviewed by Kingsley (2013). Using the literature data, the $\log_{10} C/C_0$
356 values of infectious HuNoV surrogates (i.e. MNV, TV, and FCV) and HuNoV genomes (whether
357 associated with HBGA-binding assays or not) following 2 min of HPP in simple matrices (i.e. water or
358 cell culture media) were collected. The results are shown in **Fig. 4** and **Fig. 5** for HPP at temperatures
359 of 0–4°C and 20–25°C, respectively. As described previously (Bosch et al., 2018; Kingsley, 2013), the
360 inactivation of infectious HuNoV surrogates increases with pressure applied, in a dose-dependent
361 manner. HPP led to 0.1–7.4 \log_{10} inactivation at 100–700 MPa and 0.7–6.0 \log_{10} inactivation of
362 infectious viruses at 150–450 MPa at 0–4°C and 20–25°C, respectively. We also noted a higher
363 persistence of HuNoV genomes, since a reduction to below 1 \log_{10} was achieved below 450 MPa at
364 both temperature ranges. This was confirmed by a randomized clinical trial for the inactivation of
365 infectious HuNoV in artificially contaminated oysters (Leon et al., 2011). The same authors showed
366 that GI.1 HuNoVs were completely inactivated at 600 MPa, but not at 400 MPa, after 5 minutes. The
367 capability of HBGA-binding to GII.4 and GI.1 HuNoVs gradually decreased with increased HPP.
368 There were clear differences between these two genotypes in the resistance of the viral capsid in
369 response to HPP. Here again, by quantifying HuNoV genomes following HBGA-binding assays we
370 can avoid the underestimation of the efficacy of HPP provided by estimating this based on direct
371 detection of viral genome. This is particularly true of HPP above 200–250 MPa and 450–500 MPa in
372 the two temperature ranges used for GII.4 HuNoVs and GI.1 HuNoVs, respectively. As previously
373 described (Bosch et al., 2018), the inactivation of infectious viruses by HPP is influenced by the
374 temperature, with greater efficacy in the 0–4°C temperature range. The same authors emphasize that
375 other factors, such as pH and salt concentrations within the foodstuffs, influence HPP performance in
376 virus inactivation.

377 The mechanisms of virus inactivation induced by HPP mainly occur on the viral capsid, and involve
378 the dissociation and denaturation of the capsid proteins (Bosch et al., 2018; Kingsley, 2013; Kingsley
379 et al., 2002; Lou et al., 2011). Thus, alteration of the capsid proteins can prevent attachment to the cell
380 receptors or genome injection into the host cell.

381 In conclusion: the use of HBGA-binding followed by genome detection decreases the overestimation
382 of infectious GII.4 HuNoVs and GI.1 HuNoVs for HPP above 200–250 MPa and 450–500 MPa,
383 respectively. But this approach does not appear to be suitable for predicting HuNoV infectivity in all
384 situations, especially at low doses.

385

386 **4.4. Ultraviolet light**

387 UV light is frequently used as a sanitizer for drinking water, food contact surfaces, and liquid and
388 solid food items (Food and Drug Administration, 2011). Many studies have been performed to assess
389 the virucidal efficacy of UV light, particularly in water or buffer solutions (Bosch et al., 2018; Lee et
390 al., 2008; Thurston-Enriquez et al., 2003). Log₁₀ C/C₀ values of infectious HuNoV surrogates (i.e.
391 MNV, HAV, TV, PV, and FCV) and HuNoV genomes (including a direct detection and after HBGA-
392 binding assays) as a function of UV-C radiation between 220 nm and 254 nm were collected from the
393 literature data (**Fig. 6**).

394 Infectious HuNoV surrogates are very sensitive to UV light, since less than 200 mJ/cm² is sufficient to
395 reach 6.0 log₁₀ inactivation. Conversely, HuNoV genomes are more persistent since a less than 3.0
396 log₁₀ reduction was obtained after UV disinfection at 1,000 mJ/cm². No difference appears between
397 HuNoV genomes directly quantified by RT-qPCR and HuNoV genomes quantified after HBGA-
398 binding. Walker et al. (2019) compared the inactivation by UV light of infectious GA bacteriophages
399 to that of HuNoVs, using two methods to determine capsid integrity (i.e. RNase and PGM assays
400 before genome quantification). The same authors showed that both methods could remove some of the
401 non-infectious particles, but most of them were still detected by RT-qPCR, leading to an
402 underestimation of the virucidal efficacy of UV treatment.

403 The mechanisms of virus inactivation induced by UV light have been widely investigated over the last
404 four decades. Photons are absorbed by nucleic acids (i.e. RNA and DNA) and cause several types of
405 damages involving either single bases, cross-links between adjacent bases, or cross-links between
406 nucleic acids and proteins (Shetlar, 1980; Simonet and Gantzer, 2006a; Wigginton et al., 2010, 2012b,
407 2012a). These cross-links can modify the integrity or conformation of the viral capsid (Bastin et al.,
408 2020).

409 In conclusion: estimation of HuNoV inactivation by UV treatment through the use of HBGA-binding
410 followed by genome detection does not provide any added value compared with direct detection of
411 viral genomes. Damages to the capsid proteins or RNA genomes were not sufficient to prevent
412 HBGA-binding and/or genome detection. Alternative approaches based on the measurement of
413 genome integrity, such as detection of the whole genome or both ends of the genome could reduce the
414 overestimation of infectious HuNoVs following UV treatments (Kostela et al., 2008; Li et al., 2002).

415

416 For all processing technologies (heat, chlorine, HPP, and UV light), direct genome detection very
417 clearly underestimates the virucidal efficacy of treatments. The specific selection of HuNoV particles
418 able to recognize HBGAs reduces this underestimation, but only for processing technologies inducing
419 significant changes in capsid structure, such as heating above 70°C or HPP above 450–500 MPa.
420 Conversely, this method does not prevent the overestimation of potential infectious HuNoVs after
421 heating at lower temperatures, low dose HPP or UV treatments. Even though HBGA-binding assays
422 followed by genome detection seem to limit this overestimation after chlorine disinfection, further
423 investigation, using harmonized experiments, is required to better evaluate the impact of this treatment
424 on capsid integrity.

425

426 **5. HBGA-binding to HuNoVs: a factor promoting virus transmission**

427 Virus transmission is not only affected by the inactivation of the virus but also by its adhesion to
428 different surfaces. Virus adhesion is usually explained by non-specific (i.e. electrostatic or
429 hydrophobic) interactions (Gerba and Betancourt, 2017; Vega et al., 2008). HBGA-binding to
430 HuNoVs is specific, highly diverse, and may demonstrate the integrity of the BP on the capsid.
431 Almand et al. (2017a) have classified non-HBGA ligands with specific binding interactions with
432 HuNoV capsids into four groups: simple chemical components, complex human biological
433 components, food ligands, and HBGA-like carbohydrates. All these groups are of interest to those
434 seeking to better understand virus transmission through food and the environment, since they can bind
435 to HuNoV capsids outside the host cell (Almand et al., 2017a; Etzold and Bode, 2014; Hansman et al.,
436 2012; Koromysova et al., 2015). With regard to foodstuffs, it has been demonstrated that HBGA-like

437 carbohydrates found in the digestive tissues of oysters (i.e. A and H types, and sialic acids) promote
438 the accumulation of HuNoVs in that specific organ (Le Guyader et al., 2006a; Maalouf et al., 2011,
439 2010; Tian et al., 2007a). Some food ligands were also found on the surface of fresh vegetables and
440 berries (i.e. A, H, and Lewis a types), and thus contribute to increase HuNoV adhesion (Esseili et al.,
441 2012; Gao et al., 2016; Li et al., 2012a; Zhang et al., 2019). Finally, some HBGA-like carbohydrates
442 present on bacteria found in the human gut (e.g. *E. cloacae*, lactic acid bacteria) can also participate in
443 HuNoV transmission through food and the environment. Specific binding interactions between
444 HuNoVs and environmental matrices, through HBGA-like carbohydrates, have been well described by
445 Amarasiri and Sano (2019). In addition to non-specific interactions, these specific interactions with
446 foodstuffs and bacteria can influence the attachment, behavior, and circulation of infectious HuNoVs
447 in the environment.

448 If specific adhesions to foods, through HBGA-like carbohydrates, are significant compared to non-
449 specific adhesions, HuNoVs able to interact with HBGAs should be more frequently detected in
450 matrices responsible for viral foodborne outbreaks. This may be true of food contaminated by
451 HuNoVs through the water cycle (e.g. fecal pollution of water, food that has come into contact with
452 contaminated water) where adhesion capacity is important. In the case of contamination by HuNoVs
453 through food handling operations, the most frequent mode of contamination, adhesion capacity
454 probably has a minor impact because of the high degree of virus dissemination. It is highly difficult to
455 classify food pollution origins by HuNoVs (i.e. from water cycle and others). For example, HuNoV
456 outbreaks reported as person-to-person transmission events may have initially originated in food.

457 Many HuNoV foodborne outbreaks are also due to food handling by infected people (Verhoef et al.,
458 2015). Thus, it is of interest to compare the diversity of HuNoV genotypes detected in foodstuffs to
459 that reported in infected human populations. This will potentially highlight a selection by foods based
460 on their HBGA-binding profiles. However, it is important to underline that the relative HuNoV
461 genotype prevalence in people and foods could differ between regions, based on a number of human
462 host, societal, and cultural factors, so all comparisons should take that caveat into consideration.

463 GII.4 HuNoV is the most prevalent genotype worldwide, and has caused around 70% of outbreaks
464 since 2002 (Beek et al., 2018). The ability of GII.4 HuNoVs to adapt to water/food transmission needs

465 more comprehensive study, focusing on survival and/or adhesion properties in the environment (Mans,
466 2019; Matthews et al., 2012; Verhoef et al., 2010). At the genogroup level, it has been reported that
467 waterborne outbreaks related to GI HuNoVs outnumbered those of GII HuNoVs (Matthews et al.,
468 2012). At the genotype level, GI.2 and GI.4 HuNoVs were more frequently reported in foodborne than
469 in human outbreaks from 1999 to 2004 (Verhoef et al., 2010). In studies of prevalence in foodstuffs,
470 GI HuNoVs were more frequently detected in bivalve molluscan shellfish (46%) than in infected
471 people (12%) (Verhoef et al., 2010). Moreover, GI and GII HuNoVs were detected in 43% and 88%,
472 respectively, of raw wastewaters from four municipal wastewater treatment plants (WWTPs) during
473 winter months, and in 24% and 14%, respectively, of treated wastewaters (Silva et al., 2007). These
474 same authors have suggested that WWTPs are less effective for the removal of GI HuNoVs than for
475 that of GII HuNoVs.

476 Since HBGA-binding to HuNoVs is highly specific, with multiple binding patterns and variable
477 relative affinities as a function of genotype, rather than at the genogroup level (Huang et al., 2005;
478 Shirato et al., 2008), in 2019, literature data were analyzed to determine the presence of HuNoV
479 genotypes in food matrices, whether or not they were implicated in foodborne outbreaks. The data
480 were collected by separating prevalence studies from studies of foodborne outbreaks. For the first set
481 of studies, the keywords “norovirus,” “food,” and “detection” were searched for, and a total of 441
482 records were found. Forty-three of these were selected, after the exclusion of non-relevant publications
483 (e.g. those unrelated to food, and those dealing with viral detection in water or development of
484 methods). Bivalve molluscan shellfish represented 86.3% of the total food matrices, compared with
485 13.6% for berries and vegetables. HuNoV genotypes are more rarely identified in berries and
486 vegetables, but both GI and GII HuNoVs were found in similar proportions, ranging from 5% to
487 24.3% (Brassard et al., 2012; De Keuckelaere et al., 2015; El-Senousy et al., 2013; Loutreul et al.,
488 2014; Pérez-Rodríguez et al., 2014; Stals et al., 2011). In the case of bivalve molluscan shellfish, 18
489 publications identified the HuNoV genotypes in their prevalence studies from 2003 to 2016. The data
490 are represented in **Fig. 7**.

491 For the second set of studies dedicated to HuNoVs involved in foodborne outbreaks, the keywords
492 “norovirus,” “foodborne” and “outbreak” were searched for and a total of 432 records were found.

493 Ninety of these, published between 1993 and 2019, were selected, after the exclusion of a large
494 number of publications (i.e. those that dealt with transmission by food handlers, co-outbreaks with
495 other pathogens, or waterborne outbreaks, or that did not contain information about the contaminated
496 foodstuffs involved). Of the 90 publications, only 51 (56.7%) characterized the genotypes by
497 sequencing. The proportions of bivalve molluscan shellfish, berries, vegetables, and other food items
498 implicated in outbreaks in the selected publications were 53%, 16%, 14%, and 17%, respectively. The
499 frequency of detection of each genotype for each food category is represented in **Fig. 8**.

500 Unlike the direct detection of HuNoVs in vulnerable foodstuffs using the ISO 15216 standard, which
501 is limited to the genogroup, the determination of the genotype by sequencing is used in investigations
502 of foodborne outbreaks when HuNoVs are detectable in leftover food. In the case of oysters, 23–25
503 different HuNoV genotypes were reported by Yu et al. (2015), based on molecular epidemiology and
504 temporal–geographical distribution from 1983 to 2014. The diversity of HuNoV genotypes reported in
505 oysters could be explained by the dissemination of viral particles through the effluents of municipal
506 WWTPs (or personal sanitation) located near shellfish production areas. In the case of berries and
507 vegetables, water irrigation is considered a major source of viral contamination (Kokkinos et al.,
508 2017). To better understand whether some food items could influence HuNoV transmission, HuNoV
509 genotypes characterized by prevalence studies performed on bivalve molluscan shellfish (**Fig. 7**) and
510 by several foodborne outbreak investigations (**Fig. 8**) were compared to those described in the
511 literature as responsible for human gastroenteritis cases between 2000 and 2016 (Chan et al., 2015;
512 Ferreira et al., 2010; Kumthip et al., 2018; Vega et al., 2013; Wang et al., 2012). As expected, GII.4
513 HuNoV is the most prevalent genotype reported in oysters in surveys and foodborne outbreak
514 investigations. GI.4 HuNoV is the second most prevalent genotype reported in foodstuffs.
515 Surprisingly, this genotype is not highly represented in cases of human infection, with a prevalence
516 ranging from 0.3% to 1.1% (**Table 3**). GII.7, GII.6, GI.2, and GII.3 HuNoVs are also described as
517 frequently detected in foodstuffs, but their occurrence in reported human cases is variable, ranging
518 from 0.3% to 15% (**Table 3**).

519 To summarize: some genotypes, particularly GII.4, GII.3, and GII.6 HuNoVs, are frequently identified
520 in both food and infected people. Conversely, other genotypes, such as GI.4, GI.2, and GII.7 HuNoVs,

521 are frequently detected in food, but less often characterized in infected people. This could suggest the
522 potential selection of certain HuNoV genotypes based on their adhesion capacities and/or survival in
523 the environment and in humans. However, other reasons should not be overlooked, such as the
524 detection of some less virulent strains in food, which would be less frequently isolated in clinical
525 cases. Interestingly, we may observe that the six most prevalent genotypes in food, described above,
526 belong to the A/B binding group described by Huang et al. (2005) (**Table 4**). However, GI.3, GII.1,
527 and GII.12 HuNoVs belonging to the A/B binding group are less often described in foods but were
528 frequently reported in human cases (**Table 3**). Thus, more comprehensive studies are required to
529 improve knowledge of the potential selection of some HuNoV genotypes in food through non-HBGA
530 ligands.

531 In conclusion: various non-HBGA ligands have been found in food or in the environment. It can
532 therefore be assumed that specific binding interactions between HuNoVs and HBGA-like
533 carbohydrates may have a direct influence on the adhesion capacity of HuNoVs to food matrices. This
534 may occur directly, through ligands present in food items, or indirectly, through specific bacteria
535 potentially present on food surfaces. These specific interactions in food and the environment are
536 HuNoV genogroup- or genotype-dependent, but the selection of the genogroup or genotype by non-
537 HBGA binding capacity remains unclear and needs further investigation.

538

539 **6. Conclusions**

540 Molecular methods are currently widely used to detect HuNoV genomes in surveys of food or
541 environmental matrices, but this strategy both overestimates the number of infectious HuNoVs in
542 surveys and underestimates the virucidal efficacy of processing technologies. Several studies assume
543 that HBGAs, putative attachment factors that promote HuNoV infection in host cells, could be suitable
544 for selecting potential infectious particles. However, basic knowledge is required to better define the
545 role of HBGAs during host cell infection before using HBGA-binding assays to potentially select
546 infectious HuNoVs. This review highlighted the fact that HBGA-binding followed by genome
547 detection can reduce the overestimation of infectious HuNoVs, but only for processing technologies
548 that allow significant changes to the capsid structure (e.g. heating above 70°C or HPP above 450–500

549 MPa). Conversely, this approach is not suitable for estimating the virucidal efficacy of processing
550 technologies (e.g. heating below 65–70°C, low dose HPP, UV light) that allow minor disruption of the
551 capsid. Thus, HBGA-binding assays can only select the presence of intact BP located in the viral
552 capsid, but cannot predict HuNoV infectivity.

553 In addition, a large number of non-HBGA ligands found in either food or the environment have now
554 been identified. It is widely acknowledged that some HBGA-like carbohydrates promote the adhesion
555 or accumulation of HuNoVs in food items, especially oysters and some fresh vegetables. Such
556 interactions may enhance viral transmission through food and the environment. Epidemiological data
557 indicate a trend toward the transmission of HuNoV genotypes, but the influence of specific binding
558 interactions between HuNoVs and non-HBGA ligands on the behavior, survival, and circulation
559 through the environment of viruses is still unclear and more comprehensive studies are needed.

560

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1373

1374 **FIGURE LEGENDS**

1375 **Figure 1: Capsid structure of GI.1 Norwalk virus (PDB 1IHM).** Capsid composed of 180 copies of
1376 VP1 assembled into 90 dimers (A). Dimer (B) and monomer (C) of VP1. In purple: shell domain; in
1377 orange and red: P1 subdomain; in green: P2 subdomain (Prasad et al. (1999); <http://www.jmol.org>).

1378

1379 **Figure 2: Time to reduce the first log₁₀ (TFL) of infectious HuNoV surrogates and HuNoV**
1380 **genomes as a function of temperature.** The dotted line represents the regression model of infectious
1381 HuNoV surrogates defined by Bertrand et al. (2012). The solid line represent the regression model of
1382 HuNoV genomes using eight TFL values determined from raw data obtained by Bertrand et al. (2012)
1383 and Escudero-Abarca et al. (2014). Squares represent the TFL values of HuNoV genomes quantified
1384 after HBGA-binding assays, determined from the raw data obtained by Wang and Tian (2014) and
1385 Robin et al. (2019).

1386

1387 **Figure 3: Decay of infectious HuNoV surrogates and HuNoV genomes as a function of chlorine**
1388 **disinfection.** Grey triangles, grey circles and black squares correspond to infectious HuNoV
1389 surrogates, HuNoV genomes, and HuNoV genomes after HBGA-binding, respectively (for more
1390 information about data collection, see **Table 1**). C₀: initial concentration; C: concentration obtained
1391 after chlorine treatment. The lines representing HuNoV genomes (solid line) and infectious HuNoV
1392 surrogates (dotted line) indicate decay rates using the data collected.

1393

1394 **Figure 4: Decay of infectious HuNoV surrogates and HuNoV genomes as a function of high**
1395 **pressure processing between 0°C and 4°C.** Grey triangles, grey circles, black squares and white
1396 squares correspond to infectious HuNoV surrogates, HuNoV genomes, GII.4 HuNoV genomes after
1397 HBGA-binding, and GI.1 HuNoV genomes after HBGA-binding, respectively (for more information,
1398 see **Table 1**). C₀: initial concentration; C: concentration obtained after high pressure processing. Lines
1399 representing HuNoV genomes (solid line) and infectious HuNoV surrogates (dotted line) indicate
1400 decay rates using the data collected.

1401

1402 **Figure 5: Decay of infectious HuNoV surrogates and HuNoV genomes as a function of high**
1403 **pressure processing between 20°C and 25°C.** Grey triangles, grey circles, black squares and white
1404 squares correspond to infectious HuNoV surrogates, HuNoV genomes, GII.4 HuNoV genomes after
1405 HBGA-binding, and GI.1 HuNoV genomes after HBGA-binding, respectively (for more information,
1406 see **Table 1**). C_0 : initial concentration; C : concentration obtained after high pressure processing. Lines
1407 representing HuNoV genomes (solid line) and infectious HuNoV surrogates (dotted line) indicate
1408 decay rates using the data collected.

1409

1410 **Figure 6: Decay of infectious HuNoV surrogates and HuNoV genomes as a function of UV light.**
1411 Grey triangles, grey circles, and black squares correspond to infectious HuNoV surrogates, HuNoV
1412 genomes, and HuNoV genomes after HBGA-binding, respectively (for more information, see **Table**
1413 **1**). C_0 : initial concentration; C : concentration obtained after UV. Lines representing HuNoV genomes
1414 (solid line) and infectious HuNoV surrogates (dotted line) indicate decay rates using the data collected.

1415

1416 **Figure 7: HuNoV genotypes detected in shellfish, based on 18 reports published between 2003**
1417 **and 2016.** The frequency of occurrence of each given genotype is expressed as a percentage. HuNoV
1418 genotypes with detection frequencies greater than or equal to 6% are shown in text boxes with bold
1419 borders. Adapted from Boxman et al., 2006; Cheng et al., 2005; Costantini et al., 2006; Croci et al.,
1420 2007; Hansman et al., 2008; Imamura et al., 2017, 2016; Kittigul et al., 2016, 2011; La Rosa et al.,
1421 2017; Lowmoung et al., 2017; Ma et al., 2013; Myrmel et al., 2004; Nishida et al., 2007; Pu et al.,
1422 2018, 2016; Rajko-Nenow et al., 2013; Tunyakittaveeward et al., 2019.

1423

1424 **Figure 8: HuNoV genotypes detected in shellfish, berries, vegetables, and other food items**
1425 **responsible for foodborne outbreaks worldwide, according to 51 published reports.** Each
1426 percentage corresponds to the frequency of occurrence of a given genotype, according to the reports.
1427 The six most prevalent HuNoV genotypes in foodstuffs (i.e. GII.4, GI.4, GII.7, GII.6, GI.2, and GII.3)
1428 are shown in text boxes with bold borders. GI: genogroup 1; GII: genogroup 2. For more information,
1429 see **Table 2**.

1430 **TABLES**

1431 **Table 1: Data collection related to inactivation of infectious HuNoV surrogates and reduction of**
 1432 **HuNoV genomes following the use of processing technologies.** MNV: Murine Norovirus; CaCV:
 1433 Canine Calicivirus; HAV: Hepatitis A Virus; TV: Tulane Virus; FCV: Feline Calicivirus; PV:
 1434 Poliovirus; HuNoVs: genomes directly detected by RT-qPCR; HuNoVs + HBGAs: HuNoV genomes
 1435 detected after HBGA-binding. HPP: high pressure processing. UV: ultraviolet light. The ranges used
 1436 in the respective processing technologies were as follows: heating from 50 to 80°C; chlorine
 1437 disinfection of between 0.25 and 500 mg.min.L⁻¹; HPP of 100 to 700 MPa, and 100 to 550 MPa, in the
 1438 0–4°C and 20–25°C temperature ranges, respectively; and UV light of 4 to 1,000 mJ/cm².

Processing technologies	Viruses		Values	References
Heat (Fig. 2)	Infectious surrogates	MNV	Regression models	Bertrand et al., 2012
		CaCV		
		HAV		
TV				
		FCV		
	HuNoV genomes		Regression model (8 values)	Bertrand et al., 2012 Escudero-Abarca et al., 2014
	HBGA-binding assays + HuNoV genomes		5	Robin et al., 2019 Wang and Tian, 2014
Chlorine (Fig. 3)	Infectious surrogates	MNV	20	Hirneisen and Kniel, 2013 Corrêa et al., 2012 Feliciano et al., 2012 Kitajima et al., 2010 Tung et al., 2013
			3	Tung et al., 2013
		TV	3	Hirneisen and Kniel, 2013
		HuNoV genomes		32
	HBGA-binding assays + HuNoV genomes		8	Kingsley et al., 2014 Wang and Tian, 2014
HPP, 0–4°C (Fig. 4)	Infectious surrogates	MNV	20	Cromeans et al., 2014 Kingsley et al., 2007 Li and Chen, 2015 Lou et al., 2011
			4	Cromeans et al., 2014
		TV	12	Cromeans et al., 2014 DiCaprio et al., 2019 Li et al., 2017
		HuNoV genomes		10

			Li and Chen, 2015
	HBGA-binding assays + HuNoV genomes		18 DiCaprio et al., 2019 Li et al., 2017, 2013
HPP, 20–25°C (Fig. 5)	Infectious surrogates	MNV	17 Kingsley et al., 2007 Li et al., 2013 Li and Chen, 2015 Lou et al., 2011
		FCV	3 Chen et al., 2005
		TV	8 DiCaprio et al., 2019 Li et al., 2017
	HuNoV genomes		12 Li et al., 2017 Li and Chen, 2015
	HBGA-binding assays + HuNoV genomes		23 DiCaprio et al., 2019 Li et al., 2017, 2013
UV light (Fig. 6)	Infectious surrogates	MNV	13 Park et al., 2011 Rönnqvist et al., 2014
		HAV	7 Nuanualsuwan et al., 2002
		TV	28 Araud et al., 2020 Tian et al., 2013
		PV	20 Nuanualsuwan et al., 2002 Simonet and Gantzer, 2006a Tree et al., 2005
		FCV	16 Nuanualsuwan et al., 2002 Park et al., 2011 Tree et al., 2005
	HuNoV genomes		15 Rönnqvist et al., 2014 Walker et al., 2019
	HBGA-binding assays + HuNoV genomes		13 Dancho et al., 2012 Wang and Tian, 2014 Walker et al., 2019

1439

1440 **Table 2: HuNoV genotypes associated with 51 reported foodborne outbreaks.** F: Number of times

1441 a given genotype was detected. Ref (x): References (number of publications reporting the genotype).

Genotype		Genogroup I									Genogroup II														
		1	2	3	4	5	6	7	8	9	1	2	3	4	5	6	7	8	9	11	12	13	14	17	21
Shellfish	F	7	7	5	10	3	4	2	3	3	6	4	12	15	4	8	6	2	3	3	5	2	2	3	1
	Ref (26)	Boxman et al., 2006; Cheng et al., 2005; Cho et al., 2016; Costantini et al., 2006; David et al., 2007; de Laval et al., 2011; Doyle et al., 2004; Fitzgerald et al., 2014; Gallimore et al., 2005; Huang et al., 2013; Iritani et al., 2014; Le Guyader et al., 2010, 2003; Lodo et al., 2014; Loury et al., 2015; Meghnath et al., 2019; Mori et al., 2017; Nenonen et al., 2009; Prato et al., 2004; Rajko-Nenow et al., 2014; Rasmussen et al., 2016; Shieh et al., 2000; Smith et al., 2012; Symes et al., 2007; Webby et al., 2007; Woods et al., 2016																							
Berries	F	-	1	1	3	1	1	-	-	2	-	-	-	2	-	1	3	1	-	-	-	2	-	-	-
	Ref (8)	Cotterelle et al., 2005; Einöder-Moreno et al., 2016; Falkenhorst et al., 2005; Höhne et al., 2015; Mäde et al., 2013; Maunula et al., 2009; Müller et al., 2015; Sarvikivi et al., 2012																							
Vegetables	F	-	1	-	1	-	-	-	-	-	1	-	-	4	-	1	-	-	-	-	-	-	-	-	-
	Ref (7)	Makary et al., 2009; Mesquita and Nascimento, 2009; Müller et al., 2016; Park et al., 2015a; Sharma et al., 2019; Showell et al., 2007; Wadl et al., 2010.																							
Other	F	-	-	-	1	-	-	-	-	-	1	-	5	1	1	1	-	-	-	-	-	1	2	-	
	Ref (10)	Boxman et al., 2007; Glasscock, 2007; Kobayashi et al., 2004; Mesquita et al., 2014; Morillo et al., 2012; Park et al., 2015b; Sakon et al., 2018; Watier-Grillot et al., 2017; Yu et al., 2010;																							

1442

1443 **Table 3: Estimated frequencies of HuNoV genotypes associated with foodborne outbreaks.** Data
 1444 from 5 reported outbreaks were used to calculate frequencies, which are expressed as a percentage.

Genotypes	Frequency (%)	References
GI.1	0.1	Chan et al., 2015 Ferreira et al., 2010 Kumthip et al., 2018 Vega et al., 2013 Wang et al., 2012
GI.2	0.3 - 1.8	
GI.3	0.3 - 2.7	
GI.4	0.3 - 1.1	
GI.5	0.1 - 0.6	
GI.6	0.4 - 5.5	
GI.7	0.1 - 0.7	
GI.8	0.1 - 0.3	
GI.9	< 0.1	
GII.1	2.0 - 5.4	
GII.2	0.9 - 1.7	
GII.3	0.6 - 15	
GII.4	63.4 - 87.9	
GII.5	0.3 - 0.6	
GII.6	2.3 - 8.3	
GII.7	0.9 - 1.3	
GII.8	0.1 - 1.6	
GII.9	< 0.1	
GII.10	0.1 - 0.3	
GII.11	< 0.1	
GII.12	0.3 - 2.5	
GII.13	0.6 - 2.1	
GII.14	0.1 - 0.3	
GII.15	0.1 - 0.9	
GII.16	1.5 - 0.1	
GII.17	0.1 - 3.3	
GII.18	< 0.1	
GII.19	< 0.1	
GII.20	< 0.1	
GII.21	0.1 - 0.9	

1445

1446 **Table 4: HBGA-binding profiles of HuNoV genotypes according to the three binding groups**
 1447 **described by Huang et al. (2005)** A/B: A/B binding group; Le: Lewis binding group; NB: No binding
 1448 group; ND: Not determined.

GI Genotypes	GI.1	GI.2	GI.3	GI.4	GI.5	GI.6	GI.7	GI.8	GI.9
Binding Group	A/B	A/B - Le	NB - A/B	NB - A/B	ND	ND	A/B	A/B - NB	ND
GII Genotypes	GII.1	GII.2	GII.3	GII.4	GII.5	GII.6	GII.7	GII.8	GII.9
Binding Group	A/B - NB	A/B - NB	A/B	A/B	A/B	A/B	A/B	ND	Le
GII Genotypes	GII.10	GII.11	GII.12	GII.13	GII.14	GII.15	GII.16	GII.17	GII.18
Binding Group	ND	ND	A/B	Le	NB - A/B	ND	ND	A/B	ND
GII Genotypes	GII.19	GII.20	GII.21						
Binding Group	ND	ND	Le						

1449 Adapted from Donaldson et al., 2008; Huang et al., 2005, 2003; Jin et al., 2016; Nordgren et al., 2010;
 1450 Shanker et al., 2014; Shirato, 2011.

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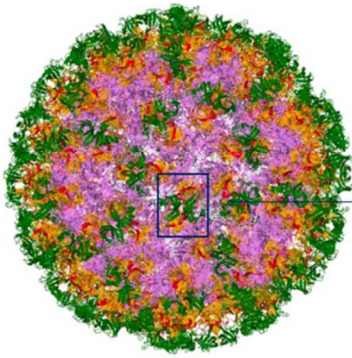
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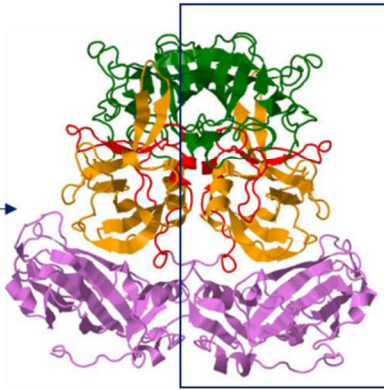
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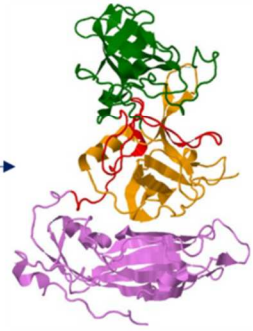
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B.



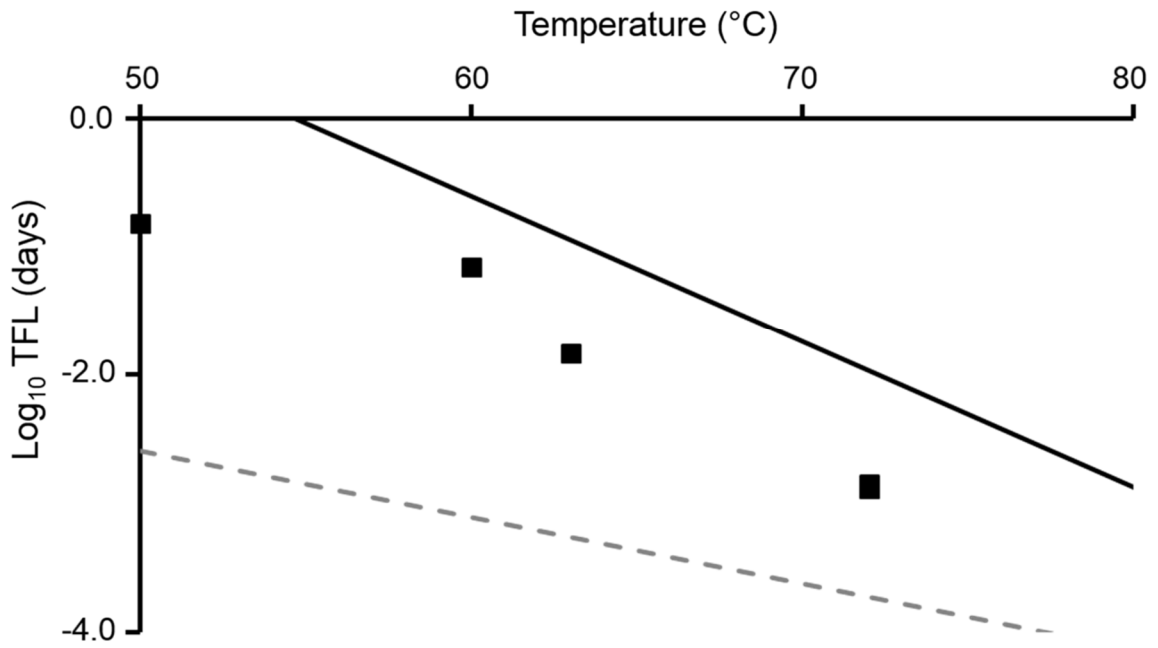
C.



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1462 **Figure 1: Capsid structure of GI.1 Norwalk virus (PDB 1IHM).**

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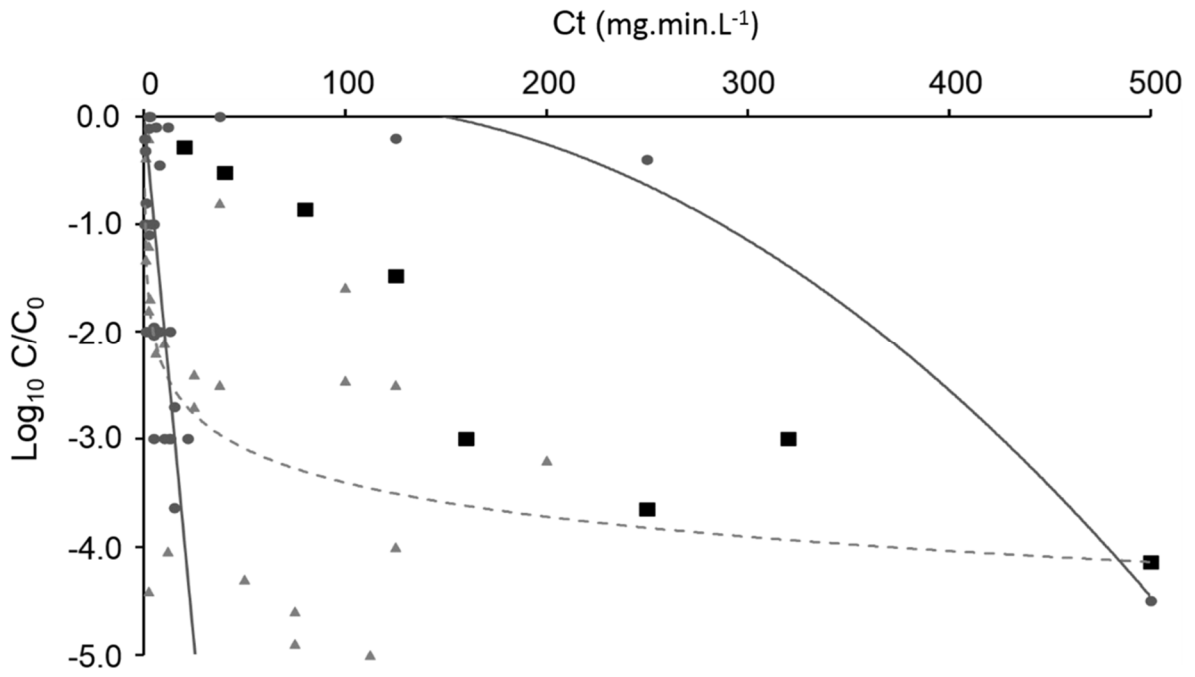
1465

Figure 2: Time to reduce the first log₁₀ (TFL) of infectious HuNoV surrogates and HuNoV

1466

genomes as a function of temperature.

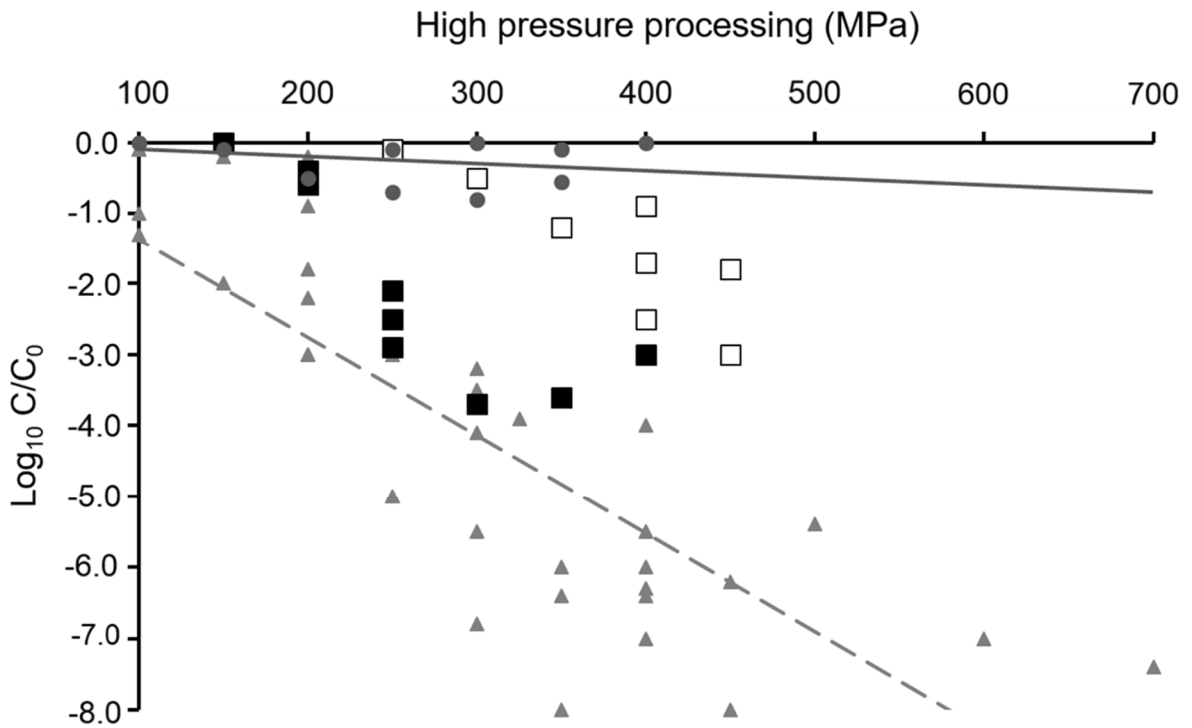
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1469 **Figure 3: Decay of infectious HuNoV surrogates and HuNoV genomes as a function of chlorine**
 1470 **disinfection.**

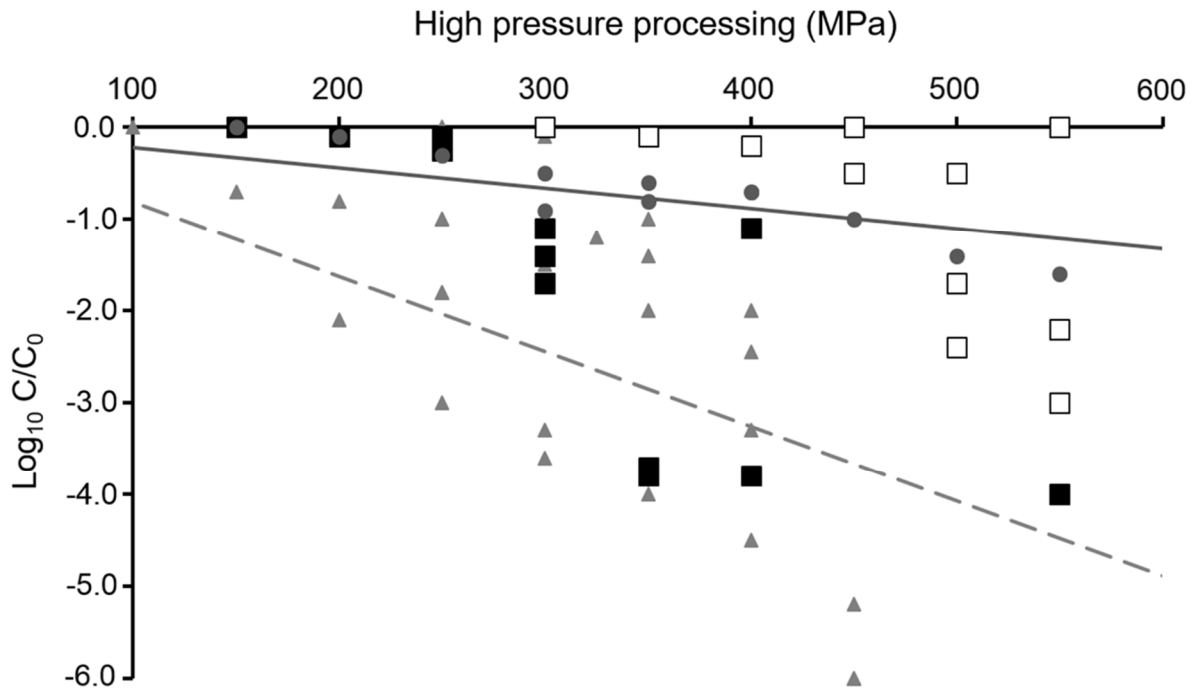
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1474 **Figure 4: Decay of infectious HuNoV surrogates and HuNoV genomes as a function of high**
1475 **pressure processing between 0°C and 4°C.**

1476

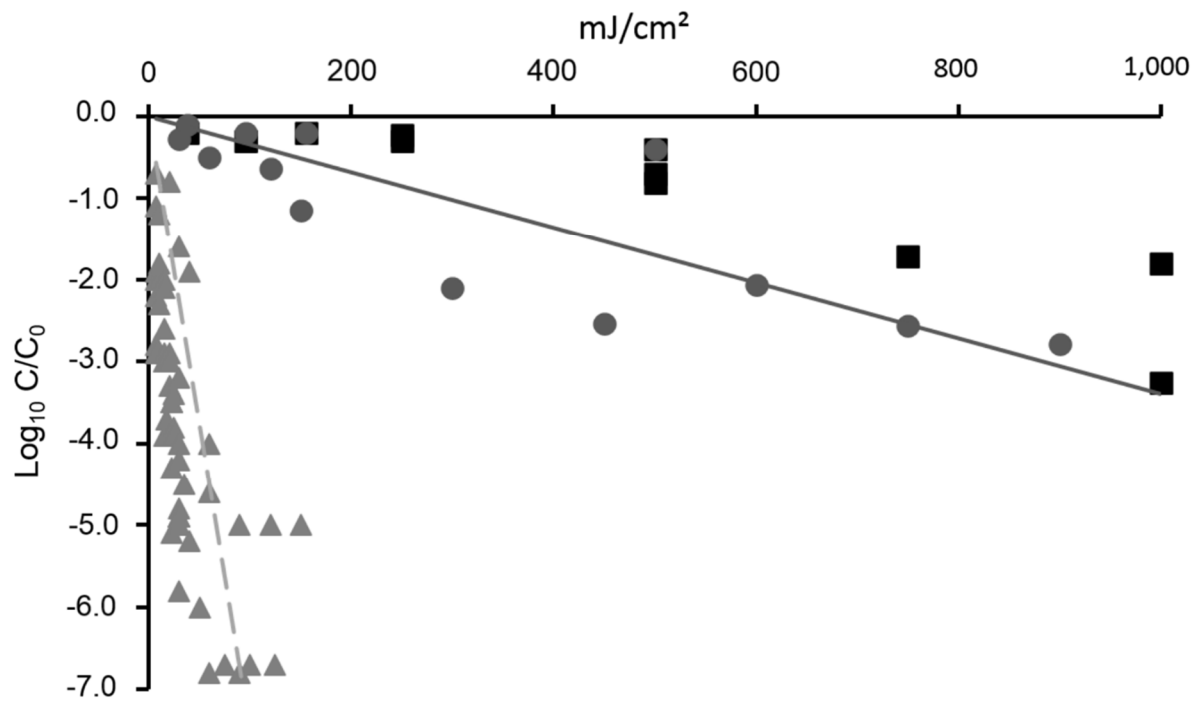


1477

1478 **Figure 5: Decay of infectious HuNoV surrogates and HuNoV genomes as a function of high**
 1479 **pressure processing between 20°C and 25°C.**

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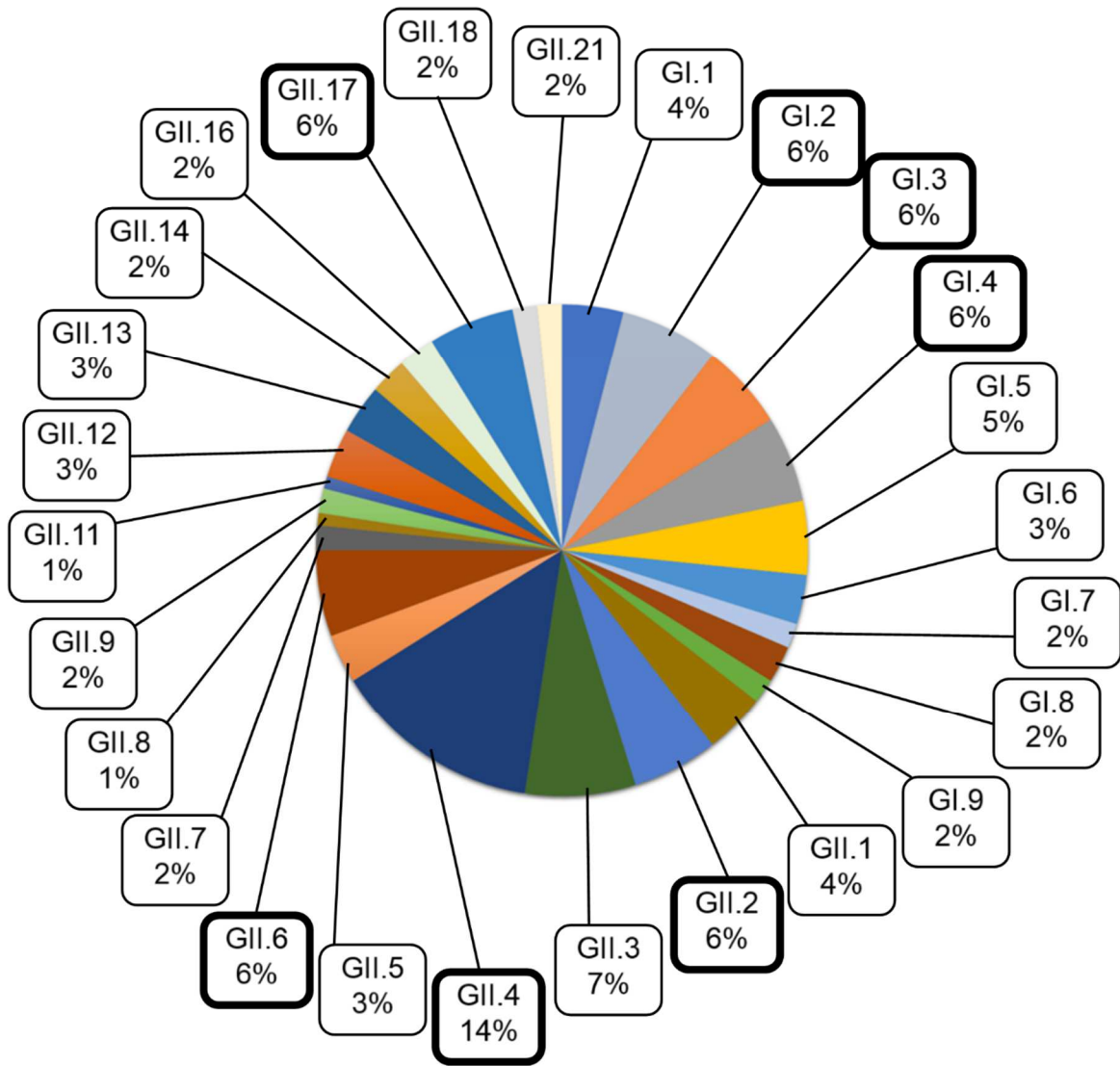


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Figure 6: Decay of infectious HuNoV surrogates and HuNoV genomes as a function of UV light.

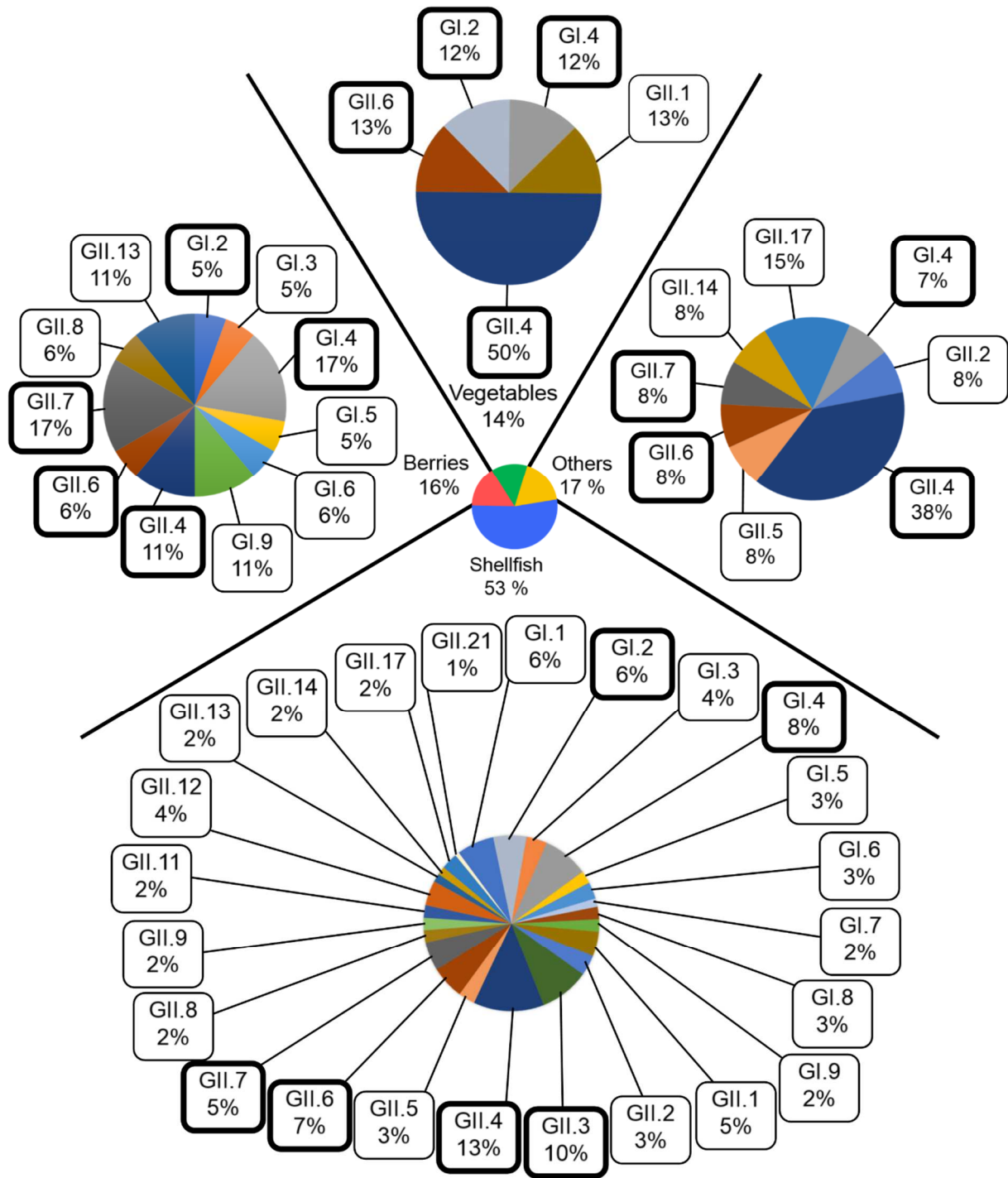
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1485

1486 **Figure 7: HuNoV genotypes detected in shellfish, based on 18 reports published between 2003**
 1487 **and 2016.**

1488



1489
 1490 **Figure 8: HuNoV genotypes detected in shellfish, berries, vegetables, and other food items**
 1491 **responsible for foodborne outbreaks worldwide according to 51 published reports.**

1492