To Whom It May Concern:

The review that follows this introductory letter is a critical assessment of the article, “Pervasive Developmental Disorders in Montreal, Quebec, Canada: Prevalence and Links With Immunizations” by Eric Fombonne, Rita Zakarian, Andrew Bennett, Linyan Meng, and Diane McLean-Heywood, published in PEDIATRICS, Vol. 118, No. 1, July 2006, pp. e139-e150 (doi:10.1542/peds.2005-2993), which I downloaded as a part of my research in this area on 16 July 2006.

In general, to clearly differentiate between my assessment comments and those of the article, the article’s printed statements are quoted in an italicized “Times New Roman” font followed by this reviewer’s remarks in indented text written in a “News Gothic MT” font, the font used in this cover letter.

Quotes from general reference articles and documents will be presented in an “Arial” font; and federal laws and statutes will be quoted in a “Lydian” font.

For those who have access to a color printer, this reviewer’s comments are made in a blue color with existing text corrections, if any, in orange.

Should anyone find any factual misrepresentations in this reviewer’s remarks, then this reviewer requests that you send the factual error along with the scientifically sound and appropriate documents that prove your point to this reviewer so that this reviewer can learn from you, incorporate that new knowledge into his understanding, and, where indicated, appropriately correct this document.

Respectfully,

Paul G. King, PhD, MS, BA
Founder,
F.A.M.E. Systems
President,
Paul G. King Consulting
AN IN-DEPTH ASSESSMENT OF:

“ABSTRACT

BACKGROUND. The prevalence of pervasive developmental disorders has increased in recent years. Links with the measles component of the measles-mumps-rubella vaccine and the cumulative exposure to thimerosal through other vaccines have been postulated.

OBJECTIVES. The purpose of this work was to estimate the pervasive developmental disorder prevalence in Montreal, Canada, in cohorts born from 1987 to 1998 and evaluate the relationship of trends in pervasive developmental disorder rates with: (1) changes in cumulative exposure to ethylmercury (thimerosal) occurring through modifications in the immunization schedule of young children and (2) trends in measles-mumps-rubella vaccination use rates and the introduction of a 2–measles-mumps-rubella dosing schedule during the study period.

METHODS. We surveyed 27749 children born from 1987 to 1998 attending 55 schools from the largest Anglophone school board. Children with pervasive developmental disorders were identified by a special needs team. The cumulative exposure by age 2 years to thimerosal was calculated for 1987–1998 birth cohorts. Ethylmercury exposure ranged from medium (100–125 µg) from 1987 to 1991 to high (200–225 µg) from 1992 to 1995 to nil from 1996 onwards when thimerosal was entirely discontinued.”

The first problem this reviewer has is that the authors’ use of the word “prevalence” in the title, and elsewhere, is misleading because all that the authors’ data allows the authors to compute is the apparent incidence rates by grade for a portion of a minority population (the English-speaking students attending a given set of schools) in a province, Quebec, where the majority of the people are French-speaking.

Second, the researcher’s “to nil from 1996 onwards when thimerosal was entirely discontinued” statement is at odds with the facts.

This is the case because the only licensed hepatitis B vaccines were Thimerosal-preserved vaccines until 2001 and these Thimerosal-preserved hepatitis B vaccines, licensed in the 1980s, were given to many children in Quebec in the 1990s – at birth, 1 dose followed by 1 or 2 others before age two and/or, in grade school, 1 to 2 doses, in the period from 1996 to 1998. [Note: In Canada, GSK’s Energix-B (hepatitis B formulation) was changed to a reduced-Thimerosal formulation on 20 December 2001. Similarly, Merck Frosst Canada & Co.’s Recombivax HB was licensed as a “preservative-free” vaccine formulation on 16 March 2001. In addition, anecdotal teacher reports have placed the Quebec immunization rate for hepatitis B as more than 25% for school-age children. Furthermore, one of the 1996 Canadian immunization “goals” for hepatitis B was universal immunization by 1997 (*Canadian Communicable Disease Report* (CCDR), Volume 24-S4, May 1997, online at: [http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/97vol23/23s4/index.html](http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/97vol23/23s4/index.html), last visited on 4 August 2006) clearly indicating that the hepatitis B vaccine was being widely used by 1996.]

In addition, Thimerosal-preserved gamma-globulin drugs and influenza vaccines may have been administered to some pregnant Canadian women during this period.
In some cases, a Thimerosal-preserved influenza vaccine may also have been administered to some children in “high risk groups” as young as 6 months of age and annually thereafter.

Thus, on average, such children, if given an annual flu shot from birth to age 16 starting in the early 1990s, may have received up to 150 µg of mercury from Thimerosal-preserved flu-shots by 1998 when they would be in Grade 7, 8 or 9.

Further, the study design seems to fail to consider the effect of the offset in time between Thimerosal dosing and the diagnosis of autism or other autism spectrum disorder (ASD; the authors’ pervasive developmental disorder [PDD]).

Finally, the medical records of these PDD-diagnosed children and their mother’s were not evaluated to ascertain the estimated total nominal dose of Thimerosal that each PDD-diagnosed child actually received from conception to the date of the study’s examination of the data.

“Measles-mumps-rubella coverage for each birth cohort was estimated through surveys of vaccination rates. The immunization schedule included a measles-mumps-rubella single dose at 12 months of age up to 1995, and a second measles-mumps-rubella dose at 18 months of age was added on after 1996.”

This reviewer notes that relying on estimates from “surveys of vaccination rates” is particularly problematic when a second dose of a vaccine is added to a schedule during the period being assessed without the immunization data for the children being studied.

This is the case because a child born in the 1990s may have received one dose and been counted as immunized up until 1996.

However, after 1996 begins, a child may be subsequently classified as being out of compliance with the guideline because he or she did not get the recommended second dose of the measles-mumps-rubella (MMR) vaccine even when the first dose had been given.

“RESULTS. We found 180 children (82.8% males) with a pervasive developmental disorder diagnosis who attended the surveyed schools, yielding a prevalence for pervasive developmental disorder of 64.9 per 10000. The prevalence for specific pervasive developmental disorder subtypes were, for autistic disorder: 21.6 of 10000; for pervasive developmental disorder not otherwise specified: 32.8 of 10,000; and for Asperger syndrome: 10.1 of 10,000. A statistically significant linear increase in pervasive developmental disorder prevalence was noted during the study period.”

First, the authors’ reported “pervasive developmental disorder of 64.9 per 10000” translates into a 1 in 154 incidence rate.

Based on “180 (181/191)” total PDD cases reported, this incidence rate implies, for 180 cases, a population of about 27,718 to 27,756 children [with an average of about 27,737 children] (or, for 181 cases, 27,868 to 27,906 [with an average of about 27,889 children]).

Since the only reported “registered” population value was “27749,” the reported incidence: a) seems reasonable and b) indicates that the included population size was, for this data, about the same as the reported “registered” value provided the included PDD total is “180” cases. [Note: Since the true PDD cases total was at least 190 (because the authors admit excluding 10 cases, the raw incidence rate for the population of “registered” students is 68.5 PDD cases per 10,000 registered students. In addition, this data would indicate that, on average, the class size should be about 2312 “registered” students in each grade)]
The “prevalence” for specific pervasive developmental disorder subtypes was reported as, for autistic disorder with a reported 61 cases, “21.6 of 10000” (see authors’ “Table 1”) or 1 “autistic disorder” case in every 463 registered students, which:

a. Is consistent with a registered school-district population of between about 28,176 and 28,306 (28,241, on average) for the 61 “autistic disorder” cases reported in three places in this study [note: this number is higher by, on average, 492 students than the “27749” value reported by the authors (“As of October 1, 2003, a total of 27749 children were registered within the LBPSB’)],

b. Indicates that the incidence number reported by the authors here may have been be incorrect (since “61” cases and a population of “27749” gives an incidence rate of about 1 in 454.9 or about 21.98 per 10,000 [indicating: i) the reported incidence should have been 21.98 or 22.0 per 10,000 children, ii) the “registered” population number reported is not the number of children considered in the study], or iii) the number of “autistic disorder” cases is not “61” [note: in 3 of the 4 instances when the number of “autistic disorder” cases is mentioned, the authors report “61” cases – however, in the authors’ “RESULTS Prevalence” section, they state (underlining added for emphasis): “Of the remaining 89 children (49.4%), 60 children (33.3%) had a diagnosis of autistic disorder, 28 children (15.6%) had a diagnosis of Asperger syndrome, and 1 child (0.6%) had CDD” – which does translate into a “21.6 per 10,000” incidence rate – this “cases” discrepancy again points to the need for all the data to be published], and, in any case,

c. Translates into a rate that less than 40% of the most recently US-reported incidence rate for “autism” of about 1 in 174 (about 55–59 “autism” [“autistic disorder”] cases per 10,000) for children “4 to 17” (see: Schieve LA, Rice C, Boyle C, Visser SN, Blumberg SJ. Mental health in the United States: Parental report of diagnosed autism in children aged 4–17 Years --- United States, 2003—2004. MMWR. May 5, 2006; 55(17): 481-486).

**Reviewer’s Crude Bar Graph**

<table>
<thead>
<tr>
<th>Number of Cases</th>
<th>Grade Range</th>
<th>Predominant Age Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>(67)</td>
<td>11-9</td>
<td>2004-2006</td>
</tr>
<tr>
<td>(49)</td>
<td>8-6</td>
<td>1998-2000</td>
</tr>
<tr>
<td>(38)</td>
<td>5-3</td>
<td>1995-1996</td>
</tr>
<tr>
<td>(26)</td>
<td>2-K</td>
<td>1990-1992</td>
</tr>
</tbody>
</table>

Reviewer’s Est. Avg. Max µg Hg

>100” “>160” “>210” “<120”
Therefore, the Canadian “autistic disorder” rate reported here for children “5 to 16” is less than half of the overall U.S. survey rate (for the total included autism cases reported [567] relative to the total included number of acceptable survey documents returned [98,475]) of about “1 in 174” children for “autism” in U.S. children “4 to 17” years of age.

Visual inspection of the authors’ reported number of students by “age group” (see authors’ “Table 1”) indicates that there does not appear to be a linear increase in autism in this population provided the number of children in each grade are roughly equal (as shown in the “Reviewer’s Crude Bar Graph”).

Moreover, if anything, the actual drop in PPD incidence rates should be even more pronounced than the crude graph indicates because, in general, population growth (including immigration) generally favors an increase in the number of children (and hence PDD cases) in a given grade as the grade declines, provided the grade registration ascertainment numbers are all nearly 100% of the grade-eligible students in the school system studied.

Based on the preceding realities, this reviewer would, at a minimum, encourage the authors to publish the actual numbers of:

a. students and
b. cases of PDDs
in each grade so that the reported incidence numbers for at least the PDD cases could be verified.

Moreover, given the discrepancy found in the reported incidence rate of 21.6 per 10000 for the 61 autistic disorder cases in this reported 27,749 population of “registered” students and the approximate incidence rate computed by this reviewer (21.98 [or 22.0 per 10,000]), this reviewer suggests the authors need to double check all of their reported cases and incidence values.

Hopefully, the authors will, in light of the preceding, publish a complete table showing all of the individual data for each diagnosis and the actual class size used for each and every grade.

“The prevalence of pervasive developmental disorder in thimerosal-free birth cohorts was significantly higher than that in thimerosal-exposed cohorts (82.7 of 10000 vs. 59.5 of 10000).”

First, as previously discussed, there were no truly Thimerosal-free cohorts in the 1987–1998 period.

Second, the observed “relative numbers” do not appear to support either:

a. A “linear increase” in PPD, or
b. Higher incidence rates in the reduced-Thimerosal cohort (those in K through 2nd grade).

Moreover, the researcher’s model failed to address the offset between Thimerosal exposure and the diagnosis of a given neurodevelopmental disorder.

Thus, the reported cohort rates seem to be at odds with the reality that the overall PPD cases were lower in the actual students in grades K through 2 (“49”) than the number of PPD cases in actual students in grades 3 through 5 (“67”) – values that seem to be at odds with the PPD incidence values reported in both of the article’s figures.
Presuming that the numbers of students in each grade are approximately equal, then
the “apparent average relative PPD for the actual student cases found would seem to be
(after setting the relative cases to “1” for the for PPD cases in grade “9 – 11”-group):
“1” for the 26 cases in the grade “9 – 11”-group; 38/26 ≡ 1.46 in the grade “6 – 8”-year-old group; 67/26 ≡ 2.58 in the grade “4 – 6” group; and “49/26” ≡ 1.88 in the grade “K – 2” group.

Based on this analysis, it would seem that the overall PPD cases found for the students
having a PPD diagnosis did, in fact, decline by about “27%” in the “grade K – 2” group
as compared to the cases of PDDs in the “grade 3 – 5” group – a decline in precisely
those students who would, on average, have gotten a lower level of Thimerosal exposure
than those in the “grade 3 – 5” group.

“Weing logistic regression models of the prevalence data, we found no significant effect of thimerosal
exposure used either as a continuous or a categorical variable. Thus, thimerosal exposure was unrelated
to the increasing trend in pervasive developmental disorder prevalence.”

Unless the actual numbers of students in each grade is significantly skewed, which does
not seem reasonable, simple inspection of the numbers of identified students in each
grade group clearly does not support the researchers “linear increase model” but they
do support a drop in incidence after the average level of Thimerosal was significantly
reduced in “1996.”

Since the authors’ fundamental assumptions seem to have been logically invalidated,
the conclusions reached seemingly must similarly be questioned, if not rejected
outright.

“These results were robust when additional analyses were performed to address possible limitations
because of the ecological nature of the data and to evaluate potential effects of misclassification on
exposure or diagnosis. Measles-mumps-rubella vaccination coverage averaged 93% during the study
interval with a statistically significant decreasing trend from 96.1% in the older birth cohorts (1988–89)
to 92.4% in younger birth cohorts (1996–1998). Thus, pervasive developmental disorder rates
significantly increased when measles-mumps-rubella vaccination uptake rates significantly decreased.
In addition, pervasive developmental disorder prevalence increased at the same rate before and after the
introduction in 1996 of the second measles-mumps-rubella dose, suggesting no increased risk of
pervasive developmental disorder associated with a 2–measles-mumps-rubella dosing schedule before
age 2 years. Results held true when additional analyses were performed to test for the potential effects
of misclassification on exposure or diagnostic status. Thus, no relationship was found between
pervasive developmental disorder rates and 1- or 2-dose measles-mumps-rubella immunization
schedule.”

Since epidemiological absence of evidence of a connection cannot be used to establish
evidence of the absence of a connection, the authors’ “no relationship was found between
pervasive developmental disorder rates and 1- or 2-dose measles-mumps-rubella immunization
schedule” does not establish that no relationship exists.

Moreover, the important relationship that needed to be addressed, but that was not, is
the relationship between: a) each case of pervasive disorder found including its
category, date of onset, and direction of progression, and b) that case’s vaccination
history with respect to the MMR vaccine including vaccination date(s), vaccine lot(s)
administered, other vaccines given, case’s weight and general health on each vaccination date, and the adverse reactions to the MMR and other vaccines, if any.

Further, the concomitant drop in the level of Thimerosal in 1996 at the same “time” the MMR was being increased from 1 dose to 2 doses may be a significant confounding factor.

Finally, only those children born close to the time that the dosing change was made (in 1994 and after) are highly likely to have received the second MMR dose at or near the recommended 18-month time – if at all.

Thus, an effect attributable to an increase in the doses of MMR may have been obscured by a larger effect from the dropping of the maximum Thimerosal exposure level by 2 years of age from “> 210” µg to “< 120” µg in 1996 with the introduction of the “preservative free” pentavalent vaccine.

“CONCLUSIONS. The prevalence of pervasive developmental disorder in Montreal was high, increasing in recent birth cohorts as found in most countries. Factors accounting for the increase include a broadening of diagnostic concepts and criteria, increased awareness and, therefore, better identification of children with pervasive developmental disorders in communities and epidemiologic surveys, and improved access to services.”

First and foremost, no valid “prevalence” estimates were, or could be, established for “Montreal.”

The nature (a English-speaking minority in Montreal – a predominately French-speaking city in a predominately French province, Quebec) and size (only 27,749 students across 12 school grades) of the population studied limits the findings to the apparent incidence of “pervasive developmental disorder in” the school system studied.

The claims of: a) “a broadening of diagnostic concepts and criteria,” b) “increased awareness” and c) increased “identification of children with pervasive developmental disorders in communities and epidemiologic surveys” have, as far as this reviewer can ascertain, only been asserted – no hard evidence has been provided for these effects in the children studied.

More importantly, in some countries, like the United States and Denmark, the authors’ “diagnostic concepts and criteria,” “increased awareness,” and increased “identification” explanations have been found, whenever scientifically assessed, not to be valid for the period from the mid-1980s to date.

In fact, in the United States’ tracking of autism by the State of California, the facts clearly indicate that the criteria for including a diagnosed, confirmed DSM “autism” case in the California autism disability database have been, if anything, slightly tightened (by effectively less than 1%) by adding inclusion criteria designed to reduce included cases because the State of California is, by law, required to provide monetary support for all included cases (see reviewer’s Appendix A, Ref. E-27).

“The findings ruled out an association between pervasive developmental disorder and either high levels of ethylmercury exposure comparable with those experienced in the United States in the 1990s or 1- or 2-dose measles-mumps-rubella vaccinations.”

Based on this reviewer’s assessment of the little actual PDD data provided in this paper (see “Reviewer’s Crude Bar Graph”), the study’s PDD number findings have not “ruled
out an association between pervasive developmental disorder” (PDD) and “high levels of ethylmercury exposure.”

In fact, the reported “PPD cases by” grade-group data seems to indicate that there was a significant drop in PPD cases in/after 1996.

This is the case even though the data on mercury level was clearly biased by the failure to include either the mercury from the Thimerosal-preserved hepatitis B vaccine that, in Quebec, was reportedly given to more than 25% of the children in the 1996-1998 age group (mostly the students in Grade K through Grade 2) or the mercury from the Thimerosal-preserved influenza vaccine that was also given to some children and/or their pregnant mothers who were high-risk-group members in the 1990s.

In instances, as the case here, where the exposure levels are variable and there is no data to account for significant sources of exposure (from the Thimerosal-preserved hepatitis B and influenza vaccines in this case), then the results (of general epidemiological studies or reported case incidence rates studies that do not thoroughly investigate the actual vaccination history of each case of PDD cases but only look at the apparent levels of exposure for the “recommended” vaccines in the population) cannot be used to disprove a linkage of the PPD case rates to the total Thimerosal exposure.

This is the case because the actual total Thimerosal exposures for the PDD cases and the non-PDD cases (controls) were neither accurately assessed nor addressed in the “studies” conducted by these authors.

Based on the reported overall PDD case data by grade groups, it would seem that there is some linkage between the “general” Thimerosal exposure levels and the PPD incidence rates by grade group.

Furthermore, this reviewer hopes that these authors will, at a minimum, fully disclose the numbers of the PDD cases and students in each grade, including any added from the special schools’ list, so that the actual incidence rates for PDDs in the schools in question can be verified and the trends, if any, in those incidence rates more accurately evaluated.

Finally, since:

a. there was no marked change in the vaccination rate for the MMR vaccine over this period, and

b. the actual MMR vaccination status of the students with the PDDs was not assessed, the association, if any, between MMR and PPD incidence cannot be reliably estimated – notwithstanding the assertions made by these authors.

**Key Words:** school-aged child • autism • Asperger syndrome • childhood disintegrative disorder • pervasive developmental disorder • prevalence • epidemiology • immunization • thimerosal • ethylmercury • measles vaccine • MMR

**Abbreviations:** PDD—pervasive developmental disorder • PDDNOS—pervasive developmental disorder not otherwise specified • CDD—childhood disintegrative disorder • MMR—measles-mumps-rubella • LBPSB—Lester B. Pearson School Board • MEQ—Ministry of Education of Quebec • DSM-IV—Diagnostic and Statistical Manual of Mental Disorders—Fourth Edition • Hib—Haemophilus influenzae type b • CI—confidence interval • OR—odds ratio • df—degrees of freedom
Pervasive developmental disorders (PDDs) are characterized by marked impairments in reciprocal social interaction, language, and communication and by the presence of repetitive/stereotypic patterns of behavior and interests. PDDs refer to a class of disorders that is composed of several diagnoses, including autistic disorder, PDD not otherwise specified (PDDNOS), Asperger syndrome, and childhood disintegrative disorder (CDD). Rett disorder has been historically listed in the PDDs to enhance differential diagnosis, but it is usually not included in studies of children with PDD. Investigations of the causes of PDDs are progressing, especially with respect to molecular genetic studies. Early intensive behavioral interventions can significantly alter developmental trajectories of preschoolers and may lead to substantial cognitive and language gains in some children. Yet, some children make little gains, and the long-term outcome of PDDs, and particularly that of autistic disorder, is still guarded. Services for children with PDDs are in great need of development in many countries, including Canada.

Epidemiologic surveys of PDDs have multiplied in recent years. Reviews and surveys conducted in the last 5 years have consistently reported prevalence rates of 0.6% for the whole PDD spectrum.”

This reviewer only notes that this “0.6% for the whole spectrum” is, coincidently, also the same as the 1 in 166 figure for autistic spectrum disorders (ASDs) in the 2004 “Autism A.L.E.R.T.” jointly issued by the United States Department of Health and Human Services (DHHS), Centers for Disease Control and Prevention (CDC), Food and Drug Administration (FDA), and the American Academy of Pediatrics (AAP).

“This roughly threefold increase in PDD prevalence over time has generated concerns about a possible epidemic, although a true secular increase in the incidence of the disorder has not yet been demonstrated. Rather, factors such as broadening of the diagnostic concepts, increased awareness of the disorder, and improved detection in surveys likely account for a substantial part of the increased prevalence.”

In general, as discussed in the review of the authors’ abstract, the declarations made in the authors’ references have been made without scientifically sound and appropriate proof that clearly established the validity of the assertions made by the authors in the references cited.

Moreover, these issues were explicitly considered and refuted in the report assessing the autism-case incidence in California that was published by the M.I.N.D. institute in 2002 (see reviewer’s Appendix A, Ref. E-27).

SINCE:
- These “incidence increase confounding” factors have been unequivocally shown not to be factors for autism and
- There has not been any significant increase in the re-diagnosis of people in their 30s, 40s, and 50s with a PDD diagnosis as would be required to logically support the authors’ assertions,

THEN, this reviewer, and others who also rely on science-based findings and not unsupported assertions based on little or no scientifically sound supporting data or logical substance, must conclude:
- The observed PDD case increases (and decreases) seen in a small sample of “Canadian” children studied by the authors of this paper are real and
- The mercury from Thimerosal is a major factor in the increases (and decreases) in the incidence rates for the PDDs found in this study of a small sample of “Canadian”
children as well as those incidence increases found by the CDC researchers in their *initial* studies (“Phase 0” and “Phase 1”) on managed-care-organization records for California children that were entered, and supposedly continue to reside, in the Vaccine Safety Datalink (VSD) database. [Note: The Geiers have consistently found epidemiological evidence of a linkage between the differences in Thimerosal exposure and differences in the rates of neurodevelopmental disorders (in all of the databases, *including the VSD*, which they have examined using the same valid epidemiological tools and study designs that the CDC has long recognized as being valid and has itself used for the various databases studied).]

“If changes in the incidence of PDDs were demonstrated, they might point toward environmental risk factors contributing to the etiology of the disorder, with or without gene interactions.”

This reviewer agrees with the authors here. In addition, this reviewer notes, *to this reviewer’s satisfaction*, both the *increases* and *decreases* in annual PDD cases track, *with an appropriate offset*, the changes in the maximum levels in mercury from Thimerosal-preserved vaccine shots in the period being studied by these authors *provided*, *for reasons that are readily apparent to this reviewer and, in the Grade 11 case, were apparent to the authors*, the uncorrected incidence data from Grade 11 and Grade K are excluded from this study (as they should have been). [Note: Instead of omitting the anomalous uncorrected data point for Grade 11, the authors of this paper “corrected” it. In the case of the anomalous Grade K data point, the authors seemingly ignored the problems associated with it and, *based on the manner in which they reported the data*, attempted to conceal the apparent class-size denominator anomaly in the PPD incidence for Grade K.]

“Few environmental exposures that occur during the prenatal period have been related to increased risk of PDDs, and such factors account for only a tiny fraction of the population risk. However, hypotheses linking vaccinations to autism have been raised since 1998. The first hypothesis implicated the measles component of the measles-mumps-rubella (MMR) vaccine that is usually given to children between 12 and 15 months of age in most countries.

*Wakefield et al.* did not hypothesize that the MMR vaccine was *causatively* linked to autism or PDDs in general.

Those researchers *only* noted a statistically significant increase in the abnormal incorporation of parts of the measles virus’ genetic material in “PPD children” diagnosed with gastrointestinal dysfunction as compared to “non-PPD children” having gastrointestinal problems.

“Subsequent epidemiologic investigations of this hypothesis have consistently failed to establish an association between MMR and autism in cohort, *case-control*, and ecological studies. Furthermore, clinical studies have also failed to identify a clinical phenotype characterizing a smaller group of autistic children presumably at risk of MMR-induced autism. Recent reviews of the MMR hypothesis by an *ad hoc* committee of the Institute of Medicine and the Cochrane collaboration concluded that the evidence favored the rejection of this hypothesis.* Yet, concerns about MMR safety have persisted among parents of autistic children and the lay public, leading to decreased uptake of the vaccine and subsequent measles epidemic outbreaks. In addition, no study has ever tested the effects of a 2-MMR dosing schedule in toddlers.

A second hypothesis implicated the cumulative exposure of young children until age 2 years to thimerosal, a vaccine stabilizer that contains 50% ethylmercury. This hypothesis is entirely distinct
from the previous one, because MMR vaccines never contained any thimerosal because it would
inactivate a live vaccine.”

In this reviewer’s view, the researchers have misstated the general “Thimerosal
hypothesis” here.

The general “Thimerosal hypothesis” holds:

The injection of Thimerosal-preserved biological drugs, indirectly into the fetus by
injecting the mother and, after birth, directly into the neonate, baby, toddler, child,
adolescent, adult and elderly person, mercury poisons all those so treated to the point
that some, after some level of exposure, exhibit all of the clinical symptoms of mercury
poisoning that are used to diagnose “autism” in children as well as the clinical
symptoms for other effects from the sub-acute mercury poisoning of children by
injecting their mothers, during pregnancy, or the children or others, at some times after
their birth, with, typically, 25- to 50- microgram doses of Thimerosal (12.5- to 25-
 microgram doses of mercury) from the Thimerosal-preserved vaccines and other
Thimerosal-preserved biological products with which they are directly or indirectly
exposed by vaccination.

Further, this reviewer also notes that if 0.01% Thimerosal is toxic to disease viruses, it
should be obvious that Thimerosal is also toxic to human cells at that level.

Moreover, actual studies have long shown that Thimerosal is up to “35” times more
toxic to human cells and tissues than it is to pathogenic bacteria (see Appendix A, Ref.
C-116).

“A review of the US immunization schedule concluded that the cumulative exposure of children at age
2 years exceeded US Food and Drug Administration and US Environmental Protection Agency
recommended safety limits and led to the suggestion in the United States to remove thimerosal from
vaccine preparations altogether.28,29 Subsequent epidemiological research on the thimerosal-autism
presumed association has been consistently negative, with cohort30–33 and ecological34,35 studies failing
to show any association.”

The researchers fail to note the initial findings of the CDC’s Verstraeten group
(published at: http://www.safeminds.org/research/library/GenerationZeroNotes.pdf),
which clearly show a strong positive correlation between the maximum level of post-
partum Thimerosal exposure and the incidence of autism.

In addition, the researchers fail to note that even the multiply iterated and intentionally
biased published CDC Verstraeten-group study found positive correlations between
Thimerosal exposure level and the incidence of some neurodevelopmental disorders.

These outcomes were observed for some vaccination time points in spite of that group’s
inappropriately assigning up to a < 37.5-microgram of mercury exposure (<75
micrograms of Thimerosal) to the “zero” group and truncating the maximum exposure
at the ≥ 62.5-microgram level — and essentially excluding those children with levels of
exposure greater than 150 micrograms (µg) of mercury (> 300 µg of Thimerosal) by 2
years of age.

Moreover, to obscure the risks observed, the values they reported were not stated in terms
of an odds ratio (OR) but rather as the relative risks (RR) “by increase per 12.5 µg of Hg
exposure from TCVs” (see, for example, Tables 3 and 4 in the published 2003
Pediatrics paper by Verstraeten et al. [ref: Verstraeten et al. Safety of Thimerosal-

For the reader’s convenience, the Tables 3 and 4 that this reviewer is referencing from the published study cited have been recreated on this page (with *bolding* added to the reported “*RR*” and “*95% CI*” values for the relative rates that are probably greater than 1.00).

“The only published ‘positive’ studies have all been performed by 1 author* and have been considered to be noncontributing because of their poor methodology.*

This reviewer notes that the authors’ statement here is factually incorrect, because the Internet-published Phase “0” and Phase “1” results found by the CDC’s “Verstraeten group” are most clearly “published ‘positive’ studies” (references: For the Phase “0” results, [http://www.safeminds.org/research/library/GenerationZeroNotes.pdf](http://www.safeminds.org/research/library/GenerationZeroNotes.pdf) and, for the Phase “1,” the findings reported in SafeMinds’ critique of the published VSD study results at: [http://www.safeminds.org/research/library/VSD_SafeMinds_critique.pdf](http://www.safeminds.org/research/library/VSD_SafeMinds_critique.pdf).

**“TABLE 3. RRs by Increase of 12.5 µg of Hg Exposure From TCVs at HMO A**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>1-Month Cumulative Hg</th>
<th>3-Month Cumulative Hg</th>
<th>7-Month Cumulative Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RR</td>
<td>95% CI</td>
<td>RR</td>
</tr>
<tr>
<td>Stammering</td>
<td>0.89</td>
<td>0.40–1.97</td>
<td>1.18</td>
</tr>
<tr>
<td>Tics</td>
<td>1.25</td>
<td>0.47–3.29</td>
<td>1.89*</td>
</tr>
<tr>
<td>Sleep disorders</td>
<td>0.79</td>
<td>0.38–1.61</td>
<td>0.93</td>
</tr>
<tr>
<td>Emotional disturbances</td>
<td>1.00</td>
<td>0.42–2.36</td>
<td>0.98</td>
</tr>
<tr>
<td>ADD</td>
<td>0.92</td>
<td>0.52–1.59</td>
<td>0.83</td>
</tr>
<tr>
<td>Speech delay</td>
<td>1.07</td>
<td>0.83–1.38</td>
<td>1.03</td>
</tr>
<tr>
<td>Speech/language delay</td>
<td>1.14</td>
<td>0.88–1.46</td>
<td>1.03</td>
</tr>
<tr>
<td>Coordination Disorders</td>
<td>1.67</td>
<td>0.78–3.57</td>
<td>1.19</td>
</tr>
</tbody>
</table>

*P < .05.

**“TABLE 4. RRs by Increase of 12.5 µg of Hg Exposure From TCVs at HMO B**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>1-Month Cumulative Hg</th>
<th>3-Month Cumulative Hg</th>
<th>7-Month Cumulative Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RR</td>
<td>95% CI</td>
<td>RR</td>
</tr>
<tr>
<td>Autism</td>
<td>1.16</td>
<td>0.78–1.71</td>
<td>1.06</td>
</tr>
<tr>
<td>Other child psychosis</td>
<td>1.03</td>
<td>0.60–1.74</td>
<td>0.93</td>
</tr>
<tr>
<td>Stammering</td>
<td>0.61</td>
<td>0.33–1.14</td>
<td>1.10</td>
</tr>
<tr>
<td>Tics</td>
<td>0.85</td>
<td>0.55–1.50</td>
<td>0.95</td>
</tr>
<tr>
<td>Sleep disorders</td>
<td>1.24</td>
<td>0.80–1.93</td>
<td>1.15</td>
</tr>
<tr>
<td>Eating disorders</td>
<td>0.90</td>
<td>0.50–1.61</td>
<td>0.97</td>
</tr>
<tr>
<td>Emotional disturbances</td>
<td>0.76</td>
<td>0.54–1.07</td>
<td>1.02</td>
</tr>
<tr>
<td>ADD</td>
<td>0.90</td>
<td>0.74–1.10</td>
<td>1.01</td>
</tr>
<tr>
<td>Language delay</td>
<td>1.06</td>
<td>0.83–1.35</td>
<td>1.13*</td>
</tr>
<tr>
<td>Speech delay</td>
<td>1.02</td>
<td>0.90–1.17</td>
<td>1.04</td>
</tr>
<tr>
<td>Language/speech delay</td>
<td>1.03</td>
<td>0.91–1.17</td>
<td>1.05</td>
</tr>
</tbody>
</table>

*P < .05.

Furthermore, other than statements in the authors’ references “25” and “38” that the referenced studies used “poor methodology,” the authors in those articles presented little,
or no, factual information to support their assertions. In addition, other anonymous critics have falsely asserted that the Geiers did not have access to the dose distribution figures (the “denominators”) that they used when the critics knew, or should have known, that the Geiers actually did have that information but did not publish those denominators because the Geiers had agreed to hold them in confidence in exchange for the government’s providing the denominators information.

Furthermore, authors of this paper failed to note the other positive epidemiological papers published in 2003, 2004, and 2005 (before this article was accepted for publication in 2006 [“Accepted Feb 15, 2006”]) in various recognized peer-reviewed journals by the “I author” (actually, 2 collaborative authors) to which they allude, including the following articles:


This reviewer notes that, as far as he can ascertain, no critiques of the epidemiological methodology used in any of these six (6) additional papers have been published in any peer-reviewed journal.

In addition, the Geiers’ study in the Vaccine Safety Datalink (VSD) database using the CDC-recommended epidemiological-study approaches in their reference-6 paper confirmed and supported their earlier findings including those questioned in this article’s references “36” and “37.”

“By and large, biological studies of ethylmercury exposure have also failed to support the thimerosal hypothesis.”

This reviewer notes that the authors have failed to report the hundreds of studies that delineate the systemic toxicity, including neurological damage, and other adverse effects caused by mercury, inorganic mercury salts and organic mercury compounds, including Thimerosal.

Collectively, these studies overwhelmingly support the validity of the Thimerosal “hypothesis” that these authors are seeking to discredit in this paper.
Table R-1: List of U.S.-licensed Thimerosal-preserved Human Biological Products Currently In Distribution in the United States, As of October 4, 1999

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Registered Trade Name</th>
<th>Licensed Manufacturer2</th>
<th>Thimerosal Concentration. In µg per mL</th>
<th>Thimerosal in µg/dose Adult (child [if less])</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allergen Extracts1</td>
<td>Various</td>
<td>Various</td>
<td>100</td>
<td>Variable (variable)</td>
</tr>
<tr>
<td>Allergen Patch Test</td>
<td>T.R.I.E. Test</td>
<td>Pharmacia Res. Cntr</td>
<td>6.5 µg per patch</td>
<td></td>
</tr>
<tr>
<td>Coccidioidin</td>
<td>Spherilin</td>
<td>ALK Labs</td>
<td>100</td>
<td>Not reported</td>
</tr>
<tr>
<td>DTaP adsorbed</td>
<td>Certiva</td>
<td>North American Vaccine</td>
<td>100</td>
<td>50 µg/0.5 mL</td>
</tr>
<tr>
<td>ACEL-IMUNE</td>
<td>Lederle</td>
<td></td>
<td>100</td>
<td>50 µg/0.5 mL</td>
</tr>
<tr>
<td>Tripedia</td>
<td>CLI</td>
<td></td>
<td>100</td>
<td>50 µg/0.5 mL</td>
</tr>
<tr>
<td>DTP adsorbed3</td>
<td>Tri-Immunol</td>
<td>Lederle</td>
<td>100</td>
<td>50 µg/0.5 mL</td>
</tr>
<tr>
<td>DTP adsorbed3</td>
<td>CLI</td>
<td></td>
<td>100</td>
<td>50 µg/0.5 mL</td>
</tr>
<tr>
<td></td>
<td>Wyeth</td>
<td></td>
<td>100</td>
<td>50 µg/0.5 mL</td>
</tr>
<tr>
<td></td>
<td>Bioport</td>
<td></td>
<td>100</td>
<td>50 µg/0.5 mL</td>
</tr>
<tr>
<td></td>
<td>MPhL</td>
<td></td>
<td>100</td>
<td>50 µg/0.5 mL</td>
</tr>
<tr>
<td></td>
<td>Wyeth</td>
<td></td>
<td>100</td>
<td>50 µg/0.5 mL</td>
</tr>
<tr>
<td>D adsorbed4</td>
<td>CLI</td>
<td></td>
<td>100</td>
<td>50 µg/0.5 mL</td>
</tr>
<tr>
<td></td>
<td>Bioport</td>
<td></td>
<td>100</td>
<td>50 µg/0.5 mL</td>
</tr>
<tr>
<td>Td adsorbed4</td>
<td>Lederle</td>
<td></td>
<td>100</td>
<td>50 µg/0.5 mL</td>
</tr>
<tr>
<td></td>
<td>MPhL</td>
<td>33</td>
<td>16.5 µg/0.5 mL</td>
<td>(8.25 µg/0.25mL)</td>
</tr>
<tr>
<td></td>
<td>Wyeth</td>
<td></td>
<td>100</td>
<td>50 µg/0.5 mL</td>
</tr>
<tr>
<td>TT fluid</td>
<td>CLI</td>
<td></td>
<td>100</td>
<td>50 µg/0.5 mL</td>
</tr>
<tr>
<td></td>
<td>Wyeth</td>
<td></td>
<td>100</td>
<td>50 µg/0.5 mL</td>
</tr>
<tr>
<td>TT adsorbed</td>
<td>CLI</td>
<td></td>
<td>100</td>
<td>50 µg/0.5 mL</td>
</tr>
<tr>
<td></td>
<td>Lederle</td>
<td></td>
<td>100</td>
<td>50 µg/0.5 mL</td>
</tr>
<tr>
<td></td>
<td>Bioport</td>
<td></td>
<td>100</td>
<td>50 µg/0.5 mL</td>
</tr>
<tr>
<td></td>
<td>MPhL</td>
<td></td>
<td>100</td>
<td>50 µg/0.5 mL</td>
</tr>
<tr>
<td></td>
<td>SSVI</td>
<td></td>
<td>100</td>
<td>50 µg/0.5 mL</td>
</tr>
<tr>
<td></td>
<td>Wyeth</td>
<td></td>
<td>100</td>
<td>50 µg/0.5 mL</td>
</tr>
<tr>
<td>T4</td>
<td>CLI</td>
<td></td>
<td>100</td>
<td>50 µg/0.5 mL</td>
</tr>
<tr>
<td></td>
<td>Bioport</td>
<td></td>
<td>100</td>
<td>50 µg/0.5 mL</td>
</tr>
<tr>
<td>DTP-HIB</td>
<td>TETRAMUNE</td>
<td>Lederle</td>
<td>100</td>
<td>50 µg/0.5 mL</td>
</tr>
<tr>
<td></td>
<td>ActHIB + DTP</td>
<td>PM</td>
<td>100</td>
<td>50 µg/0.5 mL</td>
</tr>
<tr>
<td>HIB5</td>
<td>HIBtiter</td>
<td>Lederle</td>
<td>100</td>
<td>50 µg/0.5 mL</td>
</tr>
<tr>
<td></td>
<td>(multidose only)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIB6</td>
<td>PedvaxHIB</td>
<td>Merck</td>
<td>50</td>
<td>25 µg/0.5 mL</td>
</tr>
<tr>
<td></td>
<td>(lyophilized only)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>ProHIBit</td>
<td>CLI</td>
<td>100</td>
<td>50 µg/0.5 mL</td>
</tr>
<tr>
<td></td>
<td>Energix B</td>
<td>SKB</td>
<td>50</td>
<td>50 µg/1.0 mL</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(25 µg/0.5 mL)</td>
</tr>
<tr>
<td></td>
<td>Recombivax B</td>
<td>Merck</td>
<td>50</td>
<td>50 µg/1.0 mL</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(25 µg/0.5 mL)</td>
</tr>
<tr>
<td>Influenza</td>
<td>Fluvirone</td>
<td>Medeva</td>
<td>100</td>
<td>50 µg/0.5 mL</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(25 µg/0.25 mL)</td>
</tr>
</tbody>
</table>

1 NIH NHI Report: Thimerosal [54-64-8]: Nomination to the national toxicology program. Review of the literature. April 2001, pp. 28–33
2 Manufacturers Abbreviations: CLI (Connaught Laboratories, Inc. – Pasteur Merieux Connaught USA), CLE (Connaught Laboratories, LTD), MBPI (Michigan Biologic Products Institute), MPhL (Massachusetts Public Health Biologic Laboratories), PM (Pasteur Merieux Serums et Vaccins, SA), SKB (SmithKlineBeecham Biologicals), SSVI (Swiss Serum and Vaccine Institute, Berne).
3 Allergen extracts usually contain 0.4% or 0.5% phenol. Thimerosal may be if allergen darkens in the presence of phenol (extracts of privet pollen, mushroom, grain mill dist, white potato, avocado; food extracts of corn, barley, oat, rye, and wheat). Reference: ImmunoFacts 1999.
4 Not currently distributed in the U.S.
5 HIBtiter in single-dose vials does not contain Thimerosal
6 Lyophilized PedvaxHIB no longer distributed in U.S. (personal communication Dr. Carlo Russo, Merck, 6/25/1999)
7 Diluent contains Thimerosal, unreconstituted lyophilized product does not.
Table R-1: List of U.S.-licensed Thimerosal-preserved Human Biological Products Currently In Distribution in the United States,\textsuperscript{1} As of October 4, 1999 (Cont.)

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Registered Trade Name</th>
<th>Licensed Manufacturer\textsuperscript{2}</th>
<th>Thimerosal Concentration. In µg per mL</th>
<th>Thimerosal in µg/dose Adult (child [if less])</th>
</tr>
</thead>
<tbody>
<tr>
<td>Influenza (whole viron)</td>
<td>Fluzone</td>
<td>CLI</td>
<td>100</td>
<td>50 µg/0.5 mL</td>
</tr>
<tr>
<td>Influenza (subviroin)</td>
<td>Fluzone</td>
<td>CLI</td>
<td>100</td>
<td>50 µg/0.5 mL (25 µg/0.25 mL)</td>
</tr>
<tr>
<td>Influenza</td>
<td>FluShield</td>
<td>Wyeth</td>
<td>100</td>
<td>50 µg/0.5 mL (25 µg/0.25 mL)</td>
</tr>
<tr>
<td>Influenza</td>
<td>Fluogenn</td>
<td>Parkdale</td>
<td>100</td>
<td>50 µg/0.5 mL</td>
</tr>
<tr>
<td>Japanese Encephalitis</td>
<td>JE-VAX</td>
<td>CLI (Biken)</td>
<td>70</td>
<td>70 µg/1.0 mL (35 µg/0.5 mL)</td>
</tr>
<tr>
<td>Meningococcal A\textsuperscript{3}</td>
<td>Meningococcal-A</td>
<td>CLI</td>
<td>100</td>
<td>50 µg/0.5 mL</td>
</tr>
<tr>
<td>Meningococcal C\textsuperscript{3}</td>
<td>Meningococcal-C</td>
<td>CLI</td>
<td>100</td>
<td>50 µg/0.5 mL</td>
</tr>
<tr>
<td>Meningococcal A/C\textsuperscript{4}</td>
<td>Meningococcal-A/C</td>
<td>CLI</td>
<td>100</td>
<td>50 µg/0.5 mL</td>
</tr>
<tr>
<td>Meningococcal A/C/W/Y-135 (Iyophilized)\textsuperscript{3}</td>
<td>Menimune A/C/W/Y-135</td>
<td>CLI</td>
<td>100</td>
<td>50 µg/0.5 mL</td>
</tr>
<tr>
<td>Mumps Skin Test Antigen</td>
<td>MSTA</td>
<td>CLI</td>
<td>100</td>
<td>10 µg/0.1 mL</td>
</tr>
<tr>
<td>Pneumococcal</td>
<td>Pnu-Imune 23</td>
<td>Lederle</td>
<td>100</td>
<td>50 µg/0.5 mL</td>
</tr>
<tr>
<td>Rabies\textsuperscript{4}</td>
<td>RABIE-VAX</td>
<td>CLI</td>
<td>100</td>
<td>50 µg/0.5 mL</td>
</tr>
<tr>
<td>Rabies adsorbed</td>
<td>---</td>
<td>Biopont</td>
<td>100</td>
<td>100 µg/1.0 mL (variable by weight)</td>
</tr>
<tr>
<td>Immune Globulin</td>
<td>---</td>
<td>Biopont</td>
<td>100</td>
<td>variable (by weight)</td>
</tr>
<tr>
<td>Immune Globulin\textsuperscript{5}</td>
<td>---</td>
<td>Centeon</td>
<td>100</td>
<td>variable (by weight)</td>
</tr>
<tr>
<td>Immune Globulin\textsuperscript{6}</td>
<td>---</td>
<td>Immuno-US</td>
<td>100</td>
<td>variable (by weight)</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>---</td>
<td>Abbott</td>
<td>100</td>
<td>variable (by weight)</td>
</tr>
<tr>
<td>Rho (D) Immune Globulin</td>
<td>MICRhoGAM</td>
<td>Ortho-Clinical Diagnostics</td>
<td>30-33</td>
<td>21-33/0.7-1.0mL (variable by weight)</td>
</tr>
<tr>
<td>Vaccina Immune Globulin</td>
<td>---</td>
<td>Baxter</td>
<td>100</td>
<td>variable (by weight)</td>
</tr>
</tbody>
</table>

\textsuperscript{1} NIEH NIH Report: Thimerosal [54-64-8]: Nomination to the national toxicology program. Review of the literature. April 2001, pp. 28–33

\textsuperscript{2} Manufacturers Abbreviations: CLI (Connaught Laboratories, Inc. – Pasteur Merieux Connaught USA), CLL (Connaught Laboratories, LTD), MBPI (Michigan Biologic Products Institute), MPHIL (Massachusetts Public Health Biologic Laboratories), PM (Pasteur Merieux Serums et Vaccins, SA), SKB (SmithKlineBeecham Biologicals), SSVI (Swiss Serum and Vaccine Institute, Berne).

\textsuperscript{3} No longer in active production or distribution (Dr. Thomas Lynch, Office of Blood Research and Review, 7/21/1999).

\textsuperscript{4} Produced for Department of Defense. Only one lot exists at one time, with a new lot made when the previous one becomes outdated.

These references include, \textit{but are not limited to}, the significant articles listed in this reviewer’s Appendix A and the pertinent references in them that bear on the issues of toxicity, safety, adverse reactions, and compliance with the applicable statutes and laws as they apply to Thimerosal (49.55% mercury by weight) and other mercury species in all of their uses as well as a table (see reviewer’s Table R-1 on this and the preceding pages) of the status of US-licensed human vaccines and other human Thimerosal-preserved biological products in 1999:

“Despite the accumulation of negative studies, concerns from the public have not been entirely alleviated, and fears continue to be fueled by well-publicized media accounts of a spectacular nature.”\textsuperscript{41,42}.
First, this reviewer finds that there is no “accumulation of negative studies” as the authors assert.


a. Compared to even this article, little publicized by the mainstream media,

b. More matter of fact than “spectacular,” and

c. With respect to the book, Evidence of Harm, this book’s author presents a balanced account of what has transpired and his presentation is simply factual.

“Unfortunately, these unsubstantiated claims have led to the uncontrolled development of chelation therapies of autistic children in North America.”

Here, the authors begin with an unsubstantiated “a led to b” premise, “these unsubstantiated claims have led to the uncontrolled development of chelation therapies of autistic children in North America” that ignores the reality that the nexus for the authors’ “uncontrolled development of chelation therapies of autistic children” lies in:

a. The failure of the “mainstream medical establishment” to recognize that the symptoms they were observing were the same as those proven to be caused by subacute mercury poisoning, and

b. The refusal of that establishment to recognize the value of chelation in such cases even though that establishment has wholeheartedly embraced the chelation of children to remove lead adsorbed from paint, leaded gasoline, and other exposure sources – apparently because the paint and gasoline industries are at fault and not, as in the current mercury-poisoning situation, the healthcare establishment and its practices, which have been shown to be, and are, major contributing factors to the mercury-poisoning harm observed.

“These therapies are not only of unproven efficacy, but they also can be dangerous, as unfortunately shown in the recent death of a 5-year-old boy with autism.43”

Contrary to the authors’ views, the danger is not in the chelation per se.

Factually, the “5-year-old boy” in question died because of a medical error; the wrong form of EDTA, a sodium (tetrasodium) form, was used instead of the prescribed calcium EDTA drug (the calcium disodium form of EDTA).

Thus, all that this boy’s death proved was “dangerous” was the doctor’s failure to ensure the prescribed medication was administered – a medical error – not chelation per se.

In addition, when the available intravenous chelation therapies are removed from use for heavy-metal detoxification, the risk of death from a medical error from the use of the wrong form of EDTA is virtually eliminated.

This is the reality because these other approaches generally employ the long-used and recognized chemical chelating drugs (e.g., DMSA and DMPS) or dietary supplements (e.g., NAC [N-acetyl-cysteine], ALA [alpha-lipoic acid], and vitamin C [ascorbic acid]) and/or foods (e.g., algal products like chlorella) in the form of solid dosage units
(tablets, capsules, and suppositories) and powders that are generally administered by a “knowledgeable” caring parent.

“Only 1 survey of autism spectrum disorders has thus far been performed in Canada. The authors screened 20800 children aged 4 to 6 years residing in a specific region of Nova Scotia in 1985 and, using new research diagnostic criteria, obtained a prevalence of 10.1 per 10000 children for autism.”

This reviewer only notes that the incidence of “10.1 per 10000 children for autism” matches the about “10” cases of autism per 10,000 children reported by Denmark during the period from 1982 to 1986 when, before the introduction of the MMR vaccine there in 1987, the only Thimerosal-preserved vaccine that Danish children received was the DPT shot series – similar to the national vaccination program for Thimerosal-preserved vaccines in Canada (see: Stott C, Blaxill M, Wakefield AJ. MMR and autism in perspective: The Denmark story. J Am Phys Surg. 2004 Fall; 9(3): 89-91, Figure 2, page 90).

“This survey did not generate a figure for the whole PDD spectrum, and dates back 20 years. No epidemiological survey has ever been conducted in Quebec or in other parts of Canada. As other provinces in Canada, Quebec has a universal health insurance system that ensures free access to medical care. As a result, immunization policies are effectively implemented at the population level. In the last 20 years, several changes in the official immunization schedule occurred that provided an opportunity to assess the effects, if any, of both variations in thimerosal exposure and MMR vaccine coverage on PDD rates in successive birth cohorts.”

Factually, the “several changes in the official immunization schedule” as well as the authors’ failure to include the Thimerosal-preserved hepatitis-B vaccine given to a substantial percentage of the children in Quebec and the Thimerosal-preserved inactivated influenza vaccine given to some children and pregnant women in “high risk” groups in Quebec though neither of these Thimerosal-preserved vaccines are in “in the official immunization schedule” have actually made it much more difficult to accurately assess the exact magnitude of the effect of Thimerosal-preserved vaccines on the incidence rate and distribution of PDD cases during the interval where those changes were being made.

Moreover, in contrast to the authors’ portrayal of the changes as “instantaneous” events, each Thimerosal-level change is not instantaneous but occurs over some period of time in some unspecified portion of this in the population during a “time window,” though not addressed in the article, over which the actual change occurs.

Further complicating this picture is the fact that diagnosis of a PDD case is usually delayed by some months to years from the time for the initial point in any change window.

Moreover, the authors’ refusal to find and use the ages of all the children in this school system rather than their grade further increases the assessment uncertainties in such relationship evaluation studies because, contrary to the authors’ claims, the only valid epidemiological assessments the authors could have made from the data they report collecting are grade evaluations – not the age-related evaluations that the authors claim to have made.

Based on the preceding realities, the “variations in thimerosal exposure and MMR vaccine” doses actually interfere with the “opportunity to assess the effects, if any, of both variations in thimerosal exposure and MMR vaccine coverage on PDD rates in successive birth cohorts.”
FROM THE PEN OF PAUL G. KING

Finally, because the authors have gathered grade cohort data and not birth cohort data, no scientifically valid assessments of the effects of changes in thimerosal exposure or the change in the number of MMR vaccine doses can be made “in successive birth cohorts.”

“We report here on a prevalence survey of PDDs that we conducted in 2003–2004 in a Montreal school board. The goals of this survey were to (1) generate an estimate of the prevalence of the whole PPD spectrum that could be applied to the province of Quebec for purposes of service planning, (2) estimate the prevalence of specific diagnostic subtypes within the PDD spectrum, (3) evaluate trends in prevalence rates in successive birth cohorts, (4) examine the relationship, if any, between trends in autism rates and exposure to varying levels of thimerosal during the study period, and (5) examine the relationship, if any, between trends in autism rates and MMR vaccination uptake. Compared with previous research on immunization and autism, this study uniquely examines exposure to high levels of thimerosal and also tests for the effects of a 2-dose MMR schedule before age 2 years.”

With respect to the authors’ goals, this reviewer finds that they did “(1) generate an estimate of the” incidence “of the whole PPD spectrum.”

However, because the estimates for each “putative age”/grade range or grade are not the same, no single estimate can be provided.

In addition, lacking the enrollment and total PDD cases data for each grade, this reviewer cannot precisely assess the validity of the reported PDD incidence data for each grade.

However, beginning with the total number of students stated, the number of PPD cases in each grade range (9–11, 6–8, 3–5 and K–2), the authors’ reported incidence rates for each grade (in, for example, the authors’ “Figure 1”), and an initial presumption of about a similar number of students in each of the 12 grades (about 2150 – 2700 per grade) and iterating the data without constraining the total number enrolled, it becomes apparent that:

- **For grades 3–11**, the numbers of students in each grade group is about as expected (about 2200 in average in grades 8–11, about 2400 in grades 6–8, and about 2600 in grades 3-5 or a total guesstimated enrollment of 21,600 leaving about 6150, for a total registration of “27749,” less than the expected 7800-plus (given the trends seen) for grades K–2, but

- **For grades K-2**, the guesstimated number in each grade that iterated to the total cases and individual “grade” incidences reported was “2545” for grade 2, “2734” for grade 1, but only about “1022” for grade K – a number that indicates that, for some unmentioned reason, the number of students in the Grade K group was significantly less that in any other grade groups.

Visually, the 107.6 incidence-rate value for the Grade K group also seems to be much higher than expected.

Unfortunately, the reported total number of students, “27749” is the only item in the iterative evaluation of the data that was different than the reported total (estimated total was “~ 28210–28,330” – an overall ~ 460 – 580 student excess. [Note: On 27 July 2006, this reviewer emailed Dr. Fombonne a request (see Appendix B, Exhibit 1 for a copy of this initial request) for the needed enrollment and case data for each grade so that the reason for the differences found could be addressed. A call to his number on 4 August 2006 found that Dr. Fombonne was on vacation until 14 August 2005. Calls on 15 and 16 August reached an assistant who repeatedly said she would give Dr. Fombonne this reviewer’s messages. On 18 August 2006, this reviewer sent him another email (see Appendix B, Exhibit 2 for a copy of this email request) that set a cutoff date for a reply as the end of 21 August 2006 and indicated that
a failure to respond by that date would indicate Dr. Fombonne’s unwillingness to share the requested information with this reviewer. As of 21 August 2006, Dr. Fombonne has apparently elected not to provide the requested information nor responded to any of this reviewer’s emails or telephone messages requesting the information required to verify the “incidence” rates reported in this article for which he is the contact author.

Even ignoring the enrollment difference found in the estimates, the only way this reviewer found that the reported incidence rates can have been found for a group of “28,000” enrolled students is if the numbers of students in grade K is significantly less than 2000 students – indicating that Grade K attendance is optional resulting in: a) significantly less than the “registration” seen in the other grades and/or b) a disproportionately high relative number of the registered PPD cases in the schools’ Grade K enrollment.

### Reviewer’s Guesstimated Approximate “Grade” Data

<table>
<thead>
<tr>
<th>Grade</th>
<th>Estimated Students (S)</th>
<th>Estimated Total PPD Cases (C)</th>
<th>Estimated Incidence (C/Ss x 10,000)</th>
<th>Reported Incidence (Per 10,000 Students)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>“2182”</td>
<td>“6[ 6]”</td>
<td>“27.5”</td>
<td>27.5</td>
</tr>
<tr>
<td>9</td>
<td>“2494[2244]”</td>
<td>“10[ 9]”</td>
<td>“40.1”</td>
<td>40.1</td>
</tr>
<tr>
<td>Total Estimated (Reported)</td>
<td>“26”</td>
<td>(26)</td>
<td>Avg = 37.8</td>
<td>SD  = 9.32</td>
</tr>
<tr>
<td>8</td>
<td>“2312”</td>
<td>“8”</td>
<td>“34.6”</td>
<td>34.6</td>
</tr>
<tr>
<td>7</td>
<td>“2421”</td>
<td>“16”</td>
<td>“66.1”</td>
<td>66.1</td>
</tr>
<tr>
<td>6</td>
<td>“2578”</td>
<td>“14”</td>
<td>“54.3”</td>
<td>54.3</td>
</tr>
<tr>
<td>Total Estimated (Reported)</td>
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<td>(38)</td>
<td>Avg = 51.7</td>
<td>SD  = 15.9</td>
</tr>
<tr>
<td>5</td>
<td>“2535”</td>
<td>“18”</td>
<td>“71.0”</td>
<td>70.9</td>
</tr>
<tr>
<td>4</td>
<td>“2555”</td>
<td>“25”</td>
<td>“97.8”</td>
<td>97.9</td>
</tr>
<tr>
<td>3</td>
<td>“2765”</td>
<td>“24”</td>
<td>“86.8”</td>
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<tr>
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<td>SD  = 13.6</td>
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<td>“17[16]”</td>
<td>“66.8”</td>
<td>66.8</td>
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<tr>
<td>1</td>
<td>“2734[2604]”</td>
<td>“21[20]”</td>
<td>“76.8”</td>
<td>76.8</td>
</tr>
<tr>
<td>Total Est. G 1&amp;2</td>
<td>“5278[4999]”</td>
<td>“38[36]”</td>
<td>“72.0”</td>
<td>71.8</td>
</tr>
<tr>
<td>K</td>
<td>≈1022[1208]</td>
<td>≈44[52]</td>
<td>≈107.6</td>
<td>107.6</td>
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<tr>
<td>Total Estimated (Reported)</td>
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<td>(49)</td>
<td>Avg(2) = 71.8</td>
<td>SD  = 7.07</td>
</tr>
<tr>
<td>(Registered No.)</td>
<td>“28,330[28206]”</td>
<td>“180”</td>
<td>[Avg(3) = 83.7]</td>
<td>SD  = 21.3</td>
</tr>
</tbody>
</table>

1. Guesstimates made presuming the total PDD number and reported incidence rates were okay.

[Note: This reviewer suspects that, if properly corrected for under enrollment, it would appear that the “under-registration-corrected” incidence rate for Grade K would be less than half the reported value – supporting the reality that, excluding the suspect Grade K data point, the reported Grade 1 and Grade 2 incidence data clearly indicates a PDD incidence decrease after 1996.]
Using the preceding approximations, this reviewer has constructed an approximate numbers and cases table (see “Reviewer’s Guesstimated Approximate ’Grade’ Data” table on the preceding page).

Given the reported total enrollment, it would seem that the reason the authors did not report the cases and total number of students for each grade is that their Grade K data point either:

a. Should not have been included in their analysis because:
   i. less than half of the students that could have been enrolled were, in fact, "registered" while
   ii. most of the PDD-diagnosed students in the grade-“K” age were actually enrolled, or

b. Because of points “a–i” and “a–ii,” the incidence rate for Grade K should have been corrected for the number of students that could have been enrolled but were not enrolled in Grade K.

Based on these findings, the authors should either report the data for cases and students by grade and establish that that the numbers in each grade evaluated were about the same or, if the enrollment for grade K is much lower than the enrollment for the other grades as the data seems to indicate, then, the journal that published this paper should retract it until:

- The apparent misleading reporting is appropriately corrected and
- The authors apologize for their failure to accurately evaluate the data by
  - excluding the data point for Grade K or, if a valid correction can be made,
  - correcting it for the estimated number of students that could have been enrolled in Grade K, and
- In either case, the authors seem to have misrepresented the data for Grade K.

Moreover, lacking any data on the total number of children age 5 to 16 in the province of Quebec or information about the equivalence of the vaccination uptake rates between a small percentage of the minority “Anglophone children” studied and the unstudied majority “Francophone” children, this reviewer cannot assess the applicability of these findings to the “province of Quebec” as a whole. [Note: In statistical terms, the sample size is neither sufficient in size nor representative of the population of children in the province of Quebec in grades K through 11. Because the sample is obviously not representative of the children in the province of Quebec, the authors cannot validly project the results found for the sample (expressed in terms of PDD incidence) to the prevalence of PDD in Montreal much less in all of Quebec as their statements clearly indicate that they have attempted to do.]

Thus, it is not appropriate to characterize the reported grade incidence rates as “prevalence” rates much less to extrapolate from these reported incidence rates seen in an English-speaking school district in Montreal to the city of Montreal or, worse, the “province of Quebec” as a whole.

Similarly, this reviewer finds that the authors’ second goal, “(2) estimate the prevalence of specific diagnostic subtypes within the PDD spectrum,” again seems only to have been met for the population studied and, for the reasons cited previously, not, as implicit in the authors’ statement, for the “province of Quebec” as a whole nor for the “prevalence” of any PDD in the “province of Quebec”.

Furthermore, the authors failed to provide the data for the PDD cases, total number of students of each age in each grade, or, failing that, to report the incidence rate and
cases for each age group (enabling any reader to estimate the size for each grade) in their “Table 1” information.

Given the preceding realities, this reviewer finds that the authors failed to either appropriately state or address their third goal, “(3) evaluate trends in prevalence rates in successive birth cohorts.”

All that these authors could accurately do from the data they report collecting is “evaluate trends in” incidence “rates in successive” grade “cohorts.”

Moreover, in their attempt to reach their fourth goal, “(4) examine the relationship, if any, between trends in autism rates and exposure to varying levels of thimerosal during the study period,” it appears to this reviewer that the authors:

- Failed to ensure that all of their data were unbiased or about equally biased to a small extent with respect to:
  - a. non-included cases in the grade range studied, and
  - b. persons of school age but not in school,
- Apparently, ignored the downward “trend” in the incidence rates found for grades 1 (66.8 per 10,000) and 2 (76.8 per 10,000) compared to the estimated average (92.4 per 10,000) for grades 3–4,
- Improperly included the Grade K PDD incidence value because the apparent number of students in grade K was seemingly less than half that in any other grade,
- Incorrectly modeled the data using a “linear increasing” model when the data pairs (grade and PDD incidence rate in that grade) clearly indicate that a piecewise linear model should have been used provided the biased Grade 11 and apparently biased Grade K data points were omitted from the fitting, and
- Neither the Grade 11 PDD incidence value (because, as the authors state, it is based on a significant adjustment in the number of the PDD cases included by excluding 10 PDD cases from the Grade 11 total) nor the reported Grade K PDD incidence value (because it is apparently inflated by a significant underascertainment in the number of students registered in Grade K but no parallel obvious underascertainment in the number of PDD cases in the students “registered” in Grade K) should have been included in the modeling conducted by these authors.

Further, the study approach used was not suitable to address, much less shed light on, the authors’ fifth goal, “(5) examine the relationship, if any, between trends in autism rates and MMR vaccination uptake.”

Additionally, with respect to the authors’ “(c)ompared with previous research on immunization and autism, this study uniquely examines exposure to high levels of thimerosal,” this reviewer respectfully disagrees.

This reviewer notes that the initial studies by the CDC (the “Phase 0” and “Phase 1” studies by Verstraeten et al.) published on-line by SafeMinds and the applicable general population studies published by the Geiers before this study was reported both assessed high levels of exposure for much larger populations of individuals.

Finally, since the authors did not determine the actual vaccination status (0, 1 or 2 MMR doses) for each PDD case nor assess the effect, if any, of age, weight, health, and other factors at each vaccination date, the authors could not, as they assert, properly test “for the effects of a 2-dose MMR schedule before age 2 years.”
To properly do this they would have needed, in this reviewer’s view, to segregate the PDD cases and students having no MMR, 1 MMR and 2 MMR vaccinations into separate groups, somehow correct for the confounding differences in the level of Thimerosal exposure each PDD case received, and then compare the PDD incidence rates among the MMR groups so constructed.

However, these authors did not even attempt to do the requisite data analyses.

“METHODS

Subjects

In the province of Quebec, children are educated either in English or French schools. Schools belong to school boards that are also organized according to language. The largest school board for Anglophone children in Quebec is the Lester B. Pearson School Board (LBPSB), which provides education to individuals in the south and western parts of the greater Montreal area. The LBPSB has 55 schools (45 elementary and 10 secondary) and provides education from kindergarten through grade 11. October 1, 2003, was chosen as the survey date. As of October 1, 2003, a total of 27749 children were registered within the LBPSB.”

At a minimum, the authors’ reporting should have stated or tabulated the total number of:

a. PDD cases in each grade and

b. Children in each grade

so that any reader could:

- Independently verify the grade incidence rates reported in the authors’ figures and
- Ascertain that the populations in each class:

  i. Were (or were not) about the same and

  ii. In general, increased as the grade decreased.

“Case Identification

In Quebec, children with special education needs are either integrated, segregated within a regular school, or placed within a special school. Funding, in addition to the base grant received for all students, is provided to school boards when the special needs of a student are classifiable according to criteria established by the Ministry of Education of Quebec (MEQ). Of the 10 medical or psychiatric categories allowing the school to receive extra funding from the MEQ, PDD is one of the conditions that lead to the highest incremental funding. Each year, a list of children with identified PDDs attending any one of the schools within each of the province school boards is sent to the MEQ by September 30. Using this list, the MEQ determines the amount of extra funding each school board receives to meet the needs of children with PDDs. Until 2000, children with PDDs were administratively identified only if their diagnosis was specifically stated as autism (code 51). In 2000, the category was broadened to autism spectrum disorder (code 50). In addition, the LBPSB has a special support team to monitor the progress of children with PDD in its schools. This team keeps a list of children with a PDD diagnosis, which is updated on a weekly basis. The children with PDD who are the focus of this study were identified via this list. In grade 11, several subjects (N = 10) with a PDD diagnosis were aged 17 to 21 years, as by provincial law students with special needs can extend their secondary education up to age 21. Because the count of these older subjects could not be related to a meaningful denominator, they were excluded from the survey.”
In general, this reviewer has no concerns about the information provided other than to note that no attempt was made to ascertain the number of “Anglophone” PDD cases, if any, that were located in the “LBPSB” service area who, for whatever reasons, were not attending an “LBPSB” school.

While the authors’ adjustment of the Grade 11 PDD cases may be valid, this reviewer notes that the authors did not report adjusting any of the other grades by relocating “overage” PDD children registered in a given “LBPSB” grade to their most age-appropriate grade.

Because no “meaningful denominator” could be constructed for all the PDD children “in” Grade 11, the authors should have, in this reviewer’s view, simply excluded Grade 11 from their study instead of trying to “correct” the PDD cases found there by excluding those 17 and older.

“Data

Children with a diagnosis of PDD were identified by school personnel and given a study code to preserve the anonymity of the data. Children’s diagnoses were not verified by direct assessments, but it is worth noting that a majority of these children (N = 155; 86.1%) have been diagnosed at the Montreal Children’s Hospital. School personnel further identified the diagnostic subtype using Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) diagnostic criteria, age, grade, and school the child was attending. When available, place of birth was recorded as well. Individual immunization data were not available for study subjects. Denominators used for further prevalence calculations were obtained through the LBPSB and included the total number of children (male/female) in each grade registered in any of the schools at the LBPSB. Thus, prevalence rates could be computed for each grade by dividing the number of children with a PDD diagnosis in a given grade by the corresponding denominator. Age-specific prevalence rates could not be precisely derived, because the dates of birth were only available for the PDD children but not for the whole school population.”

Since the authors admit that the age information was not available for all the children in these schools, then the “Year of birth” information on the authors’ “Figure 1” and “Figure 2” is, at best, misleading and, as such, should not have been included in the figures.

“However, we estimated the birth year of the entire school population based on their grade attendance. Thus, children in kindergarten were assumed to all be born in 1998, children in grade 1 in 1997, and so forth. We performed a check that this imputation method was correct by examining the correspondence between grade and year of birth using dates of birth from the PDD sample. In 9 of 11 comparisons, the mode of year of birth of the sample coincided with the estimated year of birth, providing confidence in our method. Although this method is not entirely accurate, the trend analysis was not influenced by potential birth cohort misclassification, as shown below.”

This reviewer again notes that the authors’ attempted rationalization for their “estimation” of “the birth year” is, as their own comparisons reportedly showed in 2 of the 11 grade comparisons made, a) inappropriate and b) “knowingly” somewhat misleading when it comes to the real years of birth for children in a given school grade.

For example, in Grade K and in grades 1 through 3, children presumed to be of an age to have received lower levels of Thimerosal may have, in fact, been a “year” older and received the higher level of Thimerosal exposure or, when a child had skipped a grade in this set, been a “year” younger and received a lower level of Thimerosal, though the grade is presumed to have received the higher level of Thimerosal.
“Immunization Exposure Data
In Quebec, the schedule of immunization is defined by the Ministry of Health and Social Services. Immunizations are administered by general practitioners, family doctors, and pediatricians in both community clinics and private offices and at no cost for the family.”

While this reviewer has no problem with what the authors state, this reviewer notes that the authors failed to mention the other Thimerosal-preserved vaccines that, though not a part of the ministry’s free “schedule of immunization,” were nonetheless available for and administered to many Quebec children up to the age of 16 during the 1990s, including a Thimerosal-preserved hepatitis B vaccine and, in some cases, a Thimerosal-preserved influenza vaccine.

“Vaccine Coverage
Vaccine coverage has traditionally been very good in Quebec. Several surveys have been performed in Quebec to evaluate the extent of adequate vaccine coverage among young children in Quebec. The definition of adequate vaccine coverage has varied between surveys, reflecting changes over time in the immunization schedule. Adequate vaccination was usually defined as the appropriate number of diphtheria-tetanus toxoids-pertussis, polio, Haemophilus influenzae type b (Hib), and MMR vaccine doses received by 24 to 30 months of age. Rates of adequate vaccine coverage have typically varied between 85% and 90% as illustrated by adequate coverage of 85.2% in 520 children aged 24 to 30 months, of 87.7% among children aged 24 to 30 months born in 1989 and 1990, and of 89.8% in 1270 children aged 24 months. Thus, the vast majority of children born in Quebec are adherent to the official immunization schedule.

Since: a) these data clearly indicate that probably not less than 10% of the children in Quebec were not vaccinated and b) vaccination is not required for school attendance, the authors should have excluded these children from the school populations in each grade unless there were children with a PDD diagnosis in the unvaccinated group.

Moreover, the authors should have, if possible: a) estimated the PDD incidence in the unvaccinated children if there were such or b), if there were not any such, reported that fact for the unvaccinated population in each grade.

Further, the authors’ failure to address the Quebec children vaccinated for hepatitis B and/or, if any, directly or indirectly given the Thimerosal-preserved inactivated influenza vaccine again misrepresents their Thimerosal-exposure findings by an unknown but possibly knowable amount – had the authors from the school district straightforwardly requested this information from the parents.

“Thimerosal/Ethylmercury Exposure
The schedule of immunization in Quebec and its changes over time can be consulted from public health official documentation. From 1985 to 1987, a combined diphtheria, pertussis (cellular), tetanus vaccine was recommended at ages 2, 4, 6, and 18 months and 4 to 6 years. Each dose contained 50 µg of thimerosal (ie, 25 µg of ethylmercury), leading to a cumulative exposure of 100 µg of ethylmercury by age 2. In 1988, a Hib vaccine was added to the schedule at 18 months of age. Because each dose contained 50 µg of thimerosal, the cumulative exposure to ethylmercury from 1988 went up to 125 µg by age 2 years. In 1992, the immunization schedule recommended that the Hib be administered at 2, 4, 6, and 18 months, with each dose containing 50 µg of thimerosal. Thus, from 1992, the cumulative exposure to ethylmercury by age 2 years reached 200 µg.
From 1987 to 1995, the polio vaccine was administered separately at 2, 4, and 18 months and 4 to 6 years. The polio vaccine did not contain any thimerosal. In 1996, the polio vaccine and the Hib vaccine were combined with diphtheria, pertussis (cellular), tetanus vaccine in a thimerosal-free pentavaccine administered at 2, 4, 6 and 18 months of age, with a polio, pertussis (cellular), tetanus booster (thimerosal-free) at 4 to 6 years. From 1998 onward, the acellular pertussis vaccine replaced the cellular vaccine in the combined vaccine. Thus, from 1996 onward, all immunizations were thimerosal-free, leading to a nil cumulative ethylmercury exposure through vaccinations by age 2 years.”

As previously discussed, the factual evidence clearly shows that the authors’ “Thus, from 1996 onward, all immunizations were thimerosal-free, leading to a nil cumulative ethylmercury exposure through vaccinations by age 2 years” is an unsupported claim because a Thimerosal-preserved hepatitis B vaccine was given to a significant portion of Quebec’s newborns and middle-school children during the period of the authors’ study.

Since a Thimerosal-free hepatitis vaccine was not licensed in Canada until 2001, some children in Grade K through 2 received between 25 µg and 75 µg (or more µg) of Thimerosal from the Thimerosal-preserved hepatitis B vaccine by age two (or later).

Further, the human influenza vaccines of this era were also Thimerosal-preserved and some grade “K–2” children may have received 12.5 to 25 µg, or more, of mercury from the Thimerosal-preserved influenza shots they received by age 3.

In addition, pregnant Canadian women receiving gammaglobulin drugs and, in some instances, a Thimerosal-preserved influenza vaccine may have transferred up to 80% of the dose of Thimerosal they received to their fetuses – from the 25 to 100+ µg of Thimerosal that the mothers may have received during pregnancy (ca. 20 to 80+ µg of Thimerosal to their fetuses, who would have weighed significantly less than a newborn baby).

This study neither addressed nor attempted to account for the impact from any of these Thimerosal sources.

“In addition, from January to March 1993, a mass immunization campaign against meningococcal disease was performed among subjects aged 6 months to 20 years. In 10% of the cases, the vaccine used contained 50 µg of thimerosal. Therefore, in a small proportion of children, the cumulative exposure to ethylmercury by age 3 may have reached 150 (instead of 125) µg of ethylmercury in children born from March 1990 to December 1991 and 225 µg of ethylmercury in children born from January 1992 to September 1992.”

This reviewer has no problem with what these authors report here but notes that the authors should have attempted to determine the total mercury exposure from Thimerosal-preserved vaccines for each of the “180” diagnosed with a PDD and reported their findings, but they did not.

Had the authors done this, their findings could have clarified the cumulative mercury exposures the PDD cases actually received, when they received the mercury (in utero or later) and the level of exposure at each vaccination time point.

From this actual exposure data, the authors may have been able to see the correlation, if any, between exposure amount and/or pattern and the actual PDD diagnosed and/or its degree of severity.
“MMR Immunization

MMR was incorporated in the official schedule of immunizations of Quebec in 1976. The recommended age for administration of MMR was 1 year of age up to 1996. Since 1996, the recommendation was to administer 2 MMR doses, at 12 and 18 months of age. Data on MMR uptake for the study period were available through the Direction de Santé Publique de la Capitale Nationale (N. Boulianne, BN, MSc, written communication, 2005). These data were routinely collected in the region of Quebec among 5-year-old children attending kindergarten during the years 1993-2004 (ie, for birth cohorts from 1988–1998). Vaccination records from children were used as the main source of information to document MMR vaccination and its date. When this information was not available, vaccination status of the children was obtained through consultation of the regional vaccination registry or else through direct contact with doctor's practices, both from community clinics or private offices. Data were unavailable for 2 birth cohorts (1987 and 1997) during the study interval. Surveys were performed annually on a total population of 35643 children, with each annual sample fluctuating in size between 2234 in 1990 to 5914 in 1993. For the 10 birth cohorts with available data, the average MMR uptake in Quebec was 93.2% during the whole period, ranging from 91.3% in the 1992 birth cohort to 96.4% in the 1989 birth cohort.”

Again, since at least 3 % to 5 % of the students probably did not receive an MMR vaccination in the period from 1987 through 1995 when one dose of vaccine was given and, after 1995, 7% to 8 % did not receive both MMR doses, it would again have been valuable to ascertain, for the “180” PDD cases, whether or not there were any PDD cases who did not get an MMR vaccination and, for those who did, whether or not the PDD diagnosis and severity, for a given level of mercury exposure, tracked the number of MMR vaccinations received (0, 1 or 2).

In addition, a multidimensional interaction matrix among the various mercury levels and exposures, MMR levels, and the PDD diagnosis and its severity could have been constructed and evaluated to ascertain the magnitude of the interaction effects and the major factor effects on the PDD diagnosed and the severity of the PDD diagnosed.

Yet, the authors again inexplicably failed to even attempt these analyses for the PDD cases identified.

“Statistical Analysis

Data were analyzed by using SAS 8.2 (SAS Institute, Cary, NC) statistical software.66 A conventional P value of .05 was chosen as a criterion for statistical significance. Conventional statistical tests were used for categorical variables. 95% confidence intervals (CIs) for prevalence estimates were calculated using the hypergeometric distribution (Fisher's exact interval). To assess the relationship between prevalence estimates and thimerosal exposure data, prevalence estimates for each successive birth cohort were modeled by using the SAS Logistic procedure and the events/trials syntax.57 Birth cohort and level of ethylmercury exposure for each birth cohort were used as predictor variables in modeling the data. Birth cohort was treated as a continuous predictor. Level of ethylmercury exposure was used either as a continuous or a categorical predictor. When used continuously, the ethylmercury level for each birth cohort was that obtained from the official immunization schedule (range: 0–225 µg). A categorical ethylmercury exposure variable was created with 3 levels (0 = zero exposure; 1 = medium exposure [ie, between 100 and 150 µg ethylmercury]; and 2 = high exposure [200 µg ethylmercury]).”

This reviewer finds the authors statements here problematic for a variety of reasons including, but not limited to:
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a. Incorrectly treating the grade data estimated (for the PDD students) and accumulated for the other students as “Birth cohort” data when, in fact it was “grade cohort” data.

b. Treating the “grade cohort” data as a “continuous predictor,” when, in fact, it is a not a “continuous predictor” because there are, for example, no grades between Grade 1 and Grade 2.

c. The failure of the authors to include the mercury exposure from all vaccines available and used on children in the schools’ population as opposed to just those “from the official immunization schedule.”

d. The incorrect creation of a “categorical ethylmercury exposure variable” with “3 levels (0 = zero exposure; 1 = medium exposure [ie, between 100 and 150 µg ethylmercury]; and 2 = high exposure [200 µg ethylmercury]),” when the exposure is to organic mercury from Thimerosal and, based on the authors’ “Figure 2” and the actual vaccines that children may have received, there were many possible levels of Thimerosal that a given child may have received with, counting the hepatitis B vaccine, not less than four general levels of mercury exposure, “< 120 µg,” “<175 µg,” “≤ 200 µg,” and “> 200 µg.”

“RESULTS

Prevalence

Of 27749 children enrolled in the LBPSB, a total of 180 children were identified with a PDD diagnosis. This translates into a prevalence of all PDD combined of 64.9 per 10000 children (95% CI: 55.8–75.0). Half of the children with PDD (N = 91; 50.6%) had a diagnosis of PDDNOS. Of the remaining 89 children (49.4%), 60 children (33.3%) had a diagnosis of autistic disorder, 28 children (15.6%) had a diagnosis of Asperger syndrome, and 1 child (0.6%) had CDD. The corresponding prevalence figures are: for autistic disorder: 21.6 of 10000 (95% CI: 16.5–27.8 of 10000); for PDDNOS: 32.8 of 10000 (95% CI: 26.4–40.2 of 10000); for Asperger syndrome: 10.1 of 10000 (95% CI: 6.7–14.6 of 10000); and for CDD: 0.4 of 10000 (95% CI: 0.0–2.0 of 10000). Table 1 illustrates the gender and age distribution by PDD diagnostic subtypes. Consistent with other studies, the data show a preponderance of males in the PDD sample (82.8%), translating into a 4.8:1 male/female ratio. Surprisingly, the male/female ratio was lower in the Asperger group than in the other 2 groups. The statistically significant age effect reflects the marked change in PDD prevalence and distribution of PDD subtypes over time (1987–1998).”

In general, this reviewer does not disagree with the statements made in this section other than to note:

a. The rate data values are incidence rate data – not prevalence data.

b. The number of children having “a diagnosis of autistic disorder” is reported as “60” here but as “61” in the authors’ “Table 1” and in two other places in the text – this apparent discrepancy should be explained and, where appropriate, corrected.

c. The lower “male/female” ratio reported for Asperger group (0.679) is not surprising to this reviewer.

d. The effects observed are grade effects and not “age” effects as the authors again assert.

e. The short period of time in this study, the failure to report the subtypes data for all grades, and the confounding by the changes in level of Thimerosal exposure all
preclude this reviewer from agreeing with the authors about their views on “the marked change in PDD prevalence and distribution of PDD subtypes.”

“> Place Holder for:

TABLE 1 Gender and Age Distribution by PDD Diagnostic Subtypes

Figure 1 provides prevalence estimates calculated separately for each grade that are used here as a proxy indicator for birth cohort. There was an important variability in prevalence estimates by grade, with the highest prevalence of 107.6 per 10000 being observed in kindergarten (eg, youngest children born in 1998), and the lowest prevalence being of 27.5 per 10000 for grade 10, among children roughly aged 16 years. Prevalence was relatively steady for grades 8 through 11. Using logistic regression, a statistically significant effect on prevalence was found for birth cohort (odds ratio [OR]: 1.10; 95% CI: 1.05–1.15), suggesting an average annual increase of 10% in prevalence rate. Inclusion of quadratic terms for birth cohort did not improve the fit of the model, suggesting that the increase of prevalence was linear during the study period.”

This reviewer has a problem with the reported PDD incidence data for Grade K, which seems to this reviewer to be an invalid assessment of the true PDD incidence rate because there appears to be a significant underascertainment in the number of children who could have attended “Kindergarten” but, for whatever reason, did not.

This reviewer also has a problem with:

- The use of grade as a “continuous” proxy for “birth cohort,” and
- The authors’ suggestion that there was “an average annual increase of 10% in prevalence rate” when, in fact, there was an apparent inverse incidence-rate relationship only between grade and PDD incidence rate for grades 4 – 10.

In addition, this reviewer also found that the Grade 11 data point should have been omitted because the incidence in Grade 11 was corrected by throwing out “over age” cases even though no such similar correction was made for any of the lower grades.

Further, when the suspect Grade K incidence rate is excluded, it is clear that, on average, the PDD incidence rate declined in Grade 1 and Grade 2 as compared to the maximum Grade 3/4 average PDD incidence rate.

Moreover, based on this reviewer’s analysis of the information provided and his rough reconstruction of the class sizes and incidences in all grades, it seems clear that the author’s reported incidence in Grade K is at least twice as large as it should have been if, as they should, the authors had corrected the denominator to all of the children eligible for Grade K instead of the number enrolled in Grade K since attendance seems to be optional for Grade K.

Had the Grade K incidence data been properly excluded, then it is obvious to this reviewer that, for grades “K–10,” a piecewise linear fit for grades “1–4” and grades “4–10” should have been used as the fitting basis for the authors’ properly corrected findings. [Note: The point for Grade 11 should have been omitted because the class actually contains some students older by more than2 years (those 19 – 21) than the nominal age for that grade when, for grades 10–K there are probably no non-PDD children who are more than two years older than the nominal age for those grades (though, because of enrollment birthdates cutoff rules, up to 25% of the children in each grade may be a year older than the nominal age for that grade). When the authors provide, as requested, the class sizes and PDD cases numbers for each grade, this reviewer will be to better ascertain what the “corrected” PPD incidence should have been for Grade K.]
Based on the omission, or approximate correction of, the Grade K PPD incidence value, it seems clear to this reviewer that, when the Thimerosal-level was reduced, the incidence rate for PDDs also dropped after the Thimerosal level dropped in spite of an approximate doubling of the MMR exposure (from 1 dose up through 1995 to 2 doses in 1996 and beyond).

“> Place Holder for:

FIGURE 1 MMR vaccine coverage and PDD rates over time.

Autism and Thimerosal
Figure 2 charts prevalence estimates and thimerosal exposure levels for each birth cohort from 1987 through 1998. A visual inspection of the data indicates that PDD rates started to increase before the change from medium (1987–1991) to high (1992–1995) exposure levels, and, even more convincingly, it shows that rates continued to rise after total discontinuation of thimerosal (1996–1998).”

After:

- Reading that a correction was applied to the Grade 11 data and discounting that point,
- Critically examining the data by groups, and
- Omitting the data point for Grade K because it is an anomalous and has an apparently low-population-enrollment-biased PDD incidence rate,

this reviewer’s visual inspection of the Grade 10 through Grade 1 data, finds, on average, that the average PDD incidence rate
- Increases from Grade 10 through Grade 4 and
- Decreases from Grade 4 through Grade 1.

Based on this visual inspection for the data points that apparently need no correction, the level of PDD falls after the level of Thimerosal declined even though the number of MMR doses was doubled.

“The highest prevalence rate was found in the 1998 thimerosal-free birth cohort. To assess this trend statistically, we first compared the average prevalence in thimerosal-free birth cohorts (1996–1998) to that of previous thimerosal-exposed birth cohorts (1987–1995). The results indicate a significantly (OR: 1.39; 95% CI: 1.01–1.92; P < .05) higher prevalence of PDD in thimerosal-free cohorts (82.7 of 10000; 95% CI: 62.0–108.0 of 10000) compared with thimerosal-exposed cohorts (59.5 of 10000; 95% CI: 49.6–70.8 of 10000).”

Until the problems with the data for Grade 11 and Grade K are addressed, these points should be omitted from any analysis.

Moreover, the cohorts that should have been compared are the grade “3–4” cohort to the grade “1–2” cohort since:
- These respectively represent adjacent approximately equal-size cohorts,
- The first consists of individuals mostly vaccinated before the significant decrease in the maximum Thimerosal exposure and
- The second consists of individuals mostly vaccinated after the significant decrease in the maximum Thimerosal.
This reviewer also finds the authors’ attempting to compare a wide-range cohort (grades 11-3) with a narrow-range cohort (grades 2-K) to be both scientifically unsound and somewhat reprehensible unless:

a. the incidence rate across both ranges is approximately constant (and it is obviously not constant for the authors’ wide “grade 11-3” range) and

b. an appropriately population-weighted comparison is made (which the authors apparently did not do in this article).

Thus, besides an apples and oranges comparison with respect to the PDD incidence values, the authors improperly included biased data points (one of which they attempted to “correct” [the Grade 11 PDD incidence rate] while both ignoring and apparently attempting to conceal the bias for the other [the Grade K PDD incidence rate]).

Based on the preceding realities, this reviewer call upon the authors to compute and report the odds ratio (OR) and their confidence intervals for the grade 4-3 cohort and the grade 2-1 cohort and to compare and explain those OR values or, failing that, to admit that their original comparisons were, for the reasons stated, inappropriate.

In addition, the use of “birth cohort” in place of “grade cohort” is also neither scientifically sound nor, based on the authors’ data, appropriate for this epidemiological dataset.

“> Place Holder for:

**FIGURE 2** Birth cohort prevalence rates and ethylmercury exposure. Dotted lines take into account the additional ethylmercury exposure because of a mass vaccination campaign against meningitis (see text).

“Logistic regression modeling of the data was then performed. Because birth cohort was associated with both level of thimerosal exposure and prevalence of PDD, birth cohort was entered in the model to adjust for its confounding effect. We then added in thimerosal exposure to the model to evaluate its specific contribution to the trend in prevalence. When thimerosal exposure was used as a continuous variable, no significant effect was found ($\chi^2 = 2.54$; degrees of freedom [df] = 1; $P = .11$). Similarly, when thimerosal exposure was entered as a categorical variable, no effect of thimerosal exposure on rates of PDD could be found ($\chi^2 = 3.24$; df = 2; $P = .20$). In both models, birth cohort exerted a significant effect on prevalence rates (OR: 1.10; 95% CI: 1.05–1.15), and adequate fit was obtained (Hosmer Lemeshow $\chi^2 = 7.90$; df = 10; $P > .50$). Thus, thimerosal exposure was unrelated to the increasing trend in PDD prevalence.”

Since, for the reasons discussed in detail, the data points the authors used and their bases are not scientifically sound and the authors’ model assumptions are obviously flawed, the findings reported by the authors here are, of necessity, not valid.

Hopefully, when the authors correct their biases and appropriately model the data, they will find what the data points (excluding the biased ones) clearly indicate, the PDD incidence rate, not “PDD prevalence” rate, is related to both the increasing and the decreasing level of Thimerosal exposure in spite of the confounding effect of a concomitant doubling of the MMR dosing when the level of Thimerosal exposure was reduced.

“We took several additional steps to assess the robustness of these results. First, to account for the slight increase of levels of thimerosal exposure for children included in the mass immunization campaign against meningococcal disease, we allocated new values of thimerosal exposure measured continuously
for the 1990 and 1991 birth cohorts (150 µg instead of 125 µg) and for the 1992 birth cohort (225 µg instead of 200 µg; see Fig 2). Because this did not affect our exposure categories, only analyses with the continuous thimerosal variable were repeated. The results remained unchanged with no statistically significant effect of thimerosal on prevalence rates of PDDs (data not shown).”

Since the basis data for this analysis include the same points that should have been excluded and used the same incorrect model, the results are as invalid as they were in the previous analysis.

Hopefully, when the authors ignore the biased PDD values for Grade 11 and Grade K, and more appropriately model the data, they will find what the data points (excluding the biased ones) clearly indicate, the PDD incidence rate is related to both the increasing and the decreasing level of Thimerosal exposure in spite of the confounding effect of a concomitant doubling of the MMR dosing when the level of Thimerosal exposure was reduced.

“Second, because of the ecological nature of the data set, individual thimerosal exposure data were not known. However, places of birth were available on all 180 of the PDD subjects. Of the 180 subjects, 158 (87.8%) were born in Quebec and were, therefore, extremely likely to have followed the immunization schedule. The proportion of children born in Quebec did not vary across the thimerosal exposure periods ($\chi^2 = 0.60; df = 2; P > .50$). Analyses were repeated on the subsample of Quebec-born subjects. Prevalence rate of PDDs increased from 40.6 of 10000 in 1987 to 102.5 of 10000 in 1998, the linear increase being statistically significant (OR: 1.10; 95% CI: 1.05–1.16; $P < .0001$). The PDD prevalence in thimerosal-free 1996–1998 birth cohorts (74.9 of 10000; 95% CI: 55.3–99.1 of 10000) was significantly higher (OR: 1.46; 95% CI: 1.04–2.05; $P = .031$) than that in thimerosal-exposed 1987–1995 birth cohorts (51.6 of 10000; 95% CI: 42.4–62.1 of 10000). Logistic regression models to test for the effects of thimerosal among Quebec-born subjects led to negative results similar to what was obtained in the whole sample. More specifically, when the effects of birth cohort were already accounted for, the effect of thimerosal was nonsignificant when treated either as a continuous exposure ($\chi^2 = 1.60; df = 1; P = .21$) or as a categorical exposure variable ($\chi^2 = 2.21; df = 2; P = .33$). In both analyses, birth cohort effects were significant (OR: 1.10; 95% CI: 1.05–1.16; $P < .0001$), and goodness-of-fit statistics were not significant, indicative of a good model fit.”

Since the basis data for this analysis include the same points that should have been excluded and used the same incorrect model, the results are as invalid as they were in the first regression analysis.

Hopefully, when the authors restrict their evaluation to the Grade 10 through Grade 1 PDD incidence values and appropriately model that data, they will find what the data points (excluding the biased ones) clearly indicate, the PDD incidence rate for the Quebec-born English-speaking children in the one school district they studied in Montreal was related to both the increasing and the decreasing level of Thimerosal exposure in spite of the confounding effect of a concomitant doubling of the MMR dosing when the level of Thimerosal exposure was reduced.

“Third, whereas exposure data were precisely calculated for each birth cohort, our method of estimation of birth cohort was indirect, raising the possibility of some misclassification on exposure. To address this problem, we rescored the year of birth by either subtracting or adding 1. This created 2 new data sets (1986–1997 and 1988–1999) with which all of the above analyses were repeated, ascribing
thimerosal exposure values of 100 µg for 1986 and of 0 µg for 1999. All of the results remained unchanged (data not shown).”

Since the basis data for this analysis include the same points that should have been excluded and used the same incorrect model, the results are as invalid as they were in the first regression analysis.

Hopefully, when the authors restrict their evaluation to the Grade 10 through Grade 1 PDD incidence values and appropriately model that data, they will find what the data points (excluding the biased ones) clearly indicate, the PDD incidence rate for the these minority English-speaking children was related to both the increasing and the decreasing level of Thimerosal exposure in spite of the confounding effect of a concomitant doubling of the MMR dosing when the level of Thimerosal exposure was reduced.

“Forth, because some diagnostic misclassification could not be entirely ruled out and is more likely to occur with more atypical forms of PDD, such as PDDNOS or Asperger syndrome, we repeated the analyses on the subsample of 61 children with a diagnosis of autistic disorder. The results were similarly negative.”

Since the basis data for this analysis include the same points that should have been excluded and use the same incorrect model, the results are as invalid as they were in the first regression analysis.

Hopefully, when the authors restrict their evaluation to the Grade 10 through Grade 1 “autistic disorder” incidence values and appropriately model that data, they will find what the data points (excluding the biased ones) clearly indicate, the PDD incidence rate for the children studied was related to both the increasing and the decreasing level of Thimerosal exposure in spite of the confounding effect of a concomitant doubling of the MMR dosing when the level of Thimerosal exposure was reduced.

“Autism and MMR
Vaccination uptake of MMR was high in Quebec, averaging 93.2% over the study years. Figure 1 illustrates the lack of relationship between PDD rates in birth cohorts from 1987 to 1998 and MMR uptake estimates. There was a slight but significant trend toward a decrease in MMR uptake from 1988 to 1998 (2 for trend = 80.7; df = 1; P < .001) with vaccine uptake dropping from 96.1% in the older birth cohorts (1988–1989) to 92.4% in younger birth cohorts (1996–1998). During the same period, a significant and linear increase in rates of PDD occurred (see above). Analyses were repeated on the subsample of 158 Quebec-born subjects who, considering the high MMR vaccine uptake in Quebec, were most likely to have been individually exposed to the MMR vaccination according to the official schedule of immunizations. As indicated above, prevalence rate of PDDs increased from 40.6 of 10000 in 1987 to 102.5 of 10000 in 1998, the linear increase being statistically significant (OR: 1.10; 95% CI: 1.05–1.16; P < .0001). Thus, PDD rates in Quebec-born children most certainly individually exposed to MMR vaccine increased at a time where MMR uptake decreased slightly, albeit significantly. As the schedule of MMR vaccination changed in 1996 with the addition of a second dose at 18 months of age, we performed 2 sets of analyses to assess whether PDD rates and MMR exposure were associated during the period of single MMR exposure only and to evaluate whether or not the introduction of a second MMR dose at 18 months of age from 1996 onward had any relationship with the trend in PDD prevalence. First, we examined the data after censoring the 1996–1998 birth cohorts to reassess the association within the context of a stable, single MMR dose exposure period. For the 1987–1995 birth
cohorts, the increase in PDD rates still showed a statistically significant increase (OR: 1.15; 95% CI: 1.07–1.23; P < .001), whereas MMR vaccine uptake showed a small but significant downward trend during the corresponding interval (2 for trend = 97.5; df = 1; P < .001) from 96.1% in older birth cohorts (1988–1989) to 92.2% in younger birth cohorts (1994–1995). Thus, the data did not support any association between the single MMR dosing at 12 months of age and the PDD rate in these birth cohorts. Second, to test for a change in the rate of increase of PDD prevalence after the introduction of the 2-dose schedule in 1996, we performed 2 separate analyses. We modeled the prevalence data with multiple logistic regression using birth cohort (continuous), period (1987–1995 and 1996–1998), and the corresponding interaction term as predictors. In this model, the hypothesis of a change over time in the rate of increase of PDDs before and after 1996 is tested by evaluating the interaction term in the model. This interaction term was nonsignificant (Wald 2 = 3.14; df = 1; P > .05), suggesting no difference in the upward trend before or after 1996. Then, we used the 1987–1995 prevalence rate series to predict what would be the prevalence estimates for the subsequent 3 years assuming that the linear increase in PDD rate observed from 1987 to 1995 remained constant. The predicted values and their associated 95% CIs for PDD rate were 108.1 of 10000 (83.41–139.86 of 10000), 123.8 of 10000 (91.01–168.14 of 10000), and 141.8 of 10000 (99.10–202.4 of 10000) for the years 1996, 1997, and 1998, respectively. Jackknife cross-validation showed very good robustness of the prediction model (data not shown). All of the actual observed prevalence estimates for these years fell below the predicted values, and in 2 instances (years 1996 and 1997), the observed prevalence estimates fell outside the predicted confidence limits. Thus, these combined results showed no indication that PDD prevalence in the 2-MMR dosing period had surpassed the values expected from the trend estimated from the single-MMR dosing period. Finally, we restricted our trend analysis to the 61 subjects with an autistic disorder diagnosis to evaluate the effects of potential diagnostic misclassification. In this subsample as well, a significant prevalence increase occurred from 1987 to 1998 (OR: 1.23; 95% CI: 1.13–1.34) at a time where the MMR uptake was decreasing significantly (see above). Thus, taken altogether, no association between MMR vaccinations (both 1 or 2 doses) and autism or PDD rates was suggested by these data.”

Since, as this reviewer has discussed, the study design is not valid, the results and findings reported here are similarly not valid.

To establish that there was no MMR effect, the authors would have needed data where the level of Thimerosal was a constant and, at random, about one-third of a significantly sized population received 2 MMR doses, one third of that population only received 1 dose, and the remaining third received no MMR vaccination.

Then, one could have looked at the excess rates, if any, of PDD incidence or distribution (more autistic disorder) in the doubly dosed children as compared to the singly dosed children and the unvaccinated children and determined the magnitude of the MMR dosing effects, if any, on the PDD incidence or distribution.

Unfortunately, in this case, when the MMR does was doubled, the level of Thimerosal was significantly reduced making it hard to estimate the effect because, given the PDD incidence variabilities reported, the population is probably too small to reliably determine the effect of increasing from one to two doses of the MMR vaccine and there are probably not enough students in this population who received the Thimerosal-preserved vaccines but did not receive at least one MMR vaccine dose.

“DISCUSSION

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Prevalence
The PDD prevalence estimate in this study was highly consistent with most recent surveys performed in several countries.\textsuperscript{6,7,10} This high figure was unexpected, because surveys that rely solely on administrative sources for case identification (e.g., medical or educational records) usually yield lower prevalence estimates.\textsuperscript{7} Moreover, the rate in the 1998 birth cohort was >1% although the lower-bound limit of the CI was in the 0.6% to 0.7% range.”

As this reviewer has previously discussed, the Grade K cohort, mislabeled the “1998 birth” cohort by the authors seemingly has an under-enrolment-biased PPD incidence, not “PDD prevalence,” because it appears that about half or less of the children eligible to enroll did enroll but that most all PDD cases enrolled because the schools provide badly needed support to the parents of those with PPD children.

This reviewer estimates that the appropriately corrected PDD incidence is on the order of 40 to 50 per 10,000 and not the author’s reported “107.6 per 10,000” value.

“Several factors could have influenced the prevalence in our study. First, diagnosis could not be directly confirmed, and it is therefore possible that PDD diagnoses were overused leading to diagnostic misclassification and overestimation of the prevalence. However, a large proportion of subjects included in this survey had been assessed and diagnosed in our pediatric hospital by different qualified professionals, limiting the extent of that possibility. In addition, the pattern of PDD diagnostic subtypes and gender correlates was fairly typical of other published samples.”

This reviewer can only agree with the authors that the observed PDD incidence rates for Grade 10 through Grade 1 were not assessment and diagnosis biased.

Since the individual data for the “PDD diagnostic subtypes,” including cases and students in each grade, were not provided, this reviewer cannot comment on their pattern or their correlation with other published data.

“Second, special schools in Montreal that provide services to children with mental retardation, sometimes associated with PDD, were not included in the study, leading to a potential underestimation of the true population rate. However, because the school board has a policy of integration of children with even severe handicaps, especially at a young age, the magnitude of this downward bias likely remained small.”

Absent any data on the numbers and ages of those PDD cases in these special schools, this reviewer can only agree that the authors’ estimates are underestimates of the true incidence except possibly for the author’s Grade 11 and Grade K PDD estimates.

“Third, because the school board is known for its inclusive and supportive approach for children with PDDs, it is possible that parents of children with PDDs may have migrated to the geographical catchment area of the school board to provide their children with better educational opportunities. Unfortunately, data about places of residence before registration to school were not available, precluding us from assessing whether selective migration into the local area by parents of children with PDDs might have occurred. The extent to which the previous possible biases cancel each other out cannot be gauged.”

This reviewer finds that the authors’ statements here seem to be reasonable and to accurately reflect the reality they have described.
“Nevertheless, the estimate of 65 of 10,000 is highly consistent with other recent studies and shows that PDDs are relatively frequent disorders among children. Also, when PDDs were broken down by subtypes, a fairly typical pattern emerged with the prevalence of PDDNOS being 1.5 times higher than that for autistic disorder, and the prevalence of CDD being extremely low, consistent with available estimates. Our PDD rate cannot be directly compared with the only previous Canadian study, because the 2 surveys differed in their case definition and methods of case ascertainment.”

Except for the misuse of the term “prevalence,” this reviewer has no problems with the authors’ statements here.

“There was a statistically significant trend for increasing prevalence rates in younger birth cohorts (as indexed by grade attendance). On average, the prevalence rate increased by 10% annually over the 12 years of the study.”

This reviewer finds that the authors’ assertions here are not substantiated by the data they report when the values for Grade 11 and Grade K are excluded.

Excluding the data from Grade 11 and Grade K, the data indicate, on average, that PDD incidence rate, by grade,

- **Increased by about 11 cases per 10,000 per grade** as the grade decreased from Grade 10 (where the average incidence rate was about 33.5 cases per 10,000) to Grade 4 (where the reported PDD rate was 97.9 cases per 10,000) and

- **Then decreased by about 9 cases per grade** as the grade continued to decrease from Grade 4 to Grade 1 (where the estimated average PDD rate is about 71.8 cases per 10,000).

If the reviewer’s estimated corrected PDD-incidence value for Grade K were to be included, the average decrease in the incidence rate for PDD cases would further drop from the Grade 1 average estimate of about 71.8 PDD cases per 10,000 children to this reviewer’s corrected Grade K guesstimates of about 40 to 50 cases per 10,000 children, or a decrease of about 20 to 30 cases per 10,000 children.

The declining PDD incidence rates for Grade 4 through Grade 1 and the estimated “corrected” Grade K incidence clearly indicate the removal of several Thimerosal-preserved vaccines in 1996 has had a significant effect on reducing the PDD incidence rates for children mostly born two to three years, or later, after several Thimerosal-preserved vaccines were replaced by a single combined Thimerosal-free vaccine.

“This finding is consistent with trends in other studies that have repeatedly shown increasing prevalence rates in younger birth cohorts in the last 15 years. It cannot be concluded from this data whether a genuine increase in the incidence of the disorder in the population occurred during the study period, or increased ascertainment and broadened diagnostic criteria, or a combination of both factors applied.”

This reviewer finds that the authors’ remarks here are at odds with the realities contained in the data.

Moreover, since there were no significant changes in “ascertainment and broadened diagnostic criteria” from 1994 onward, and the PDD incidence rates, not “prevalence rates” (as the authors assert), appear to have decreased for the children born in 1996 and later, this reviewer suggests that the authors need to revise their remarks here.
“Nevertheless, 4 factors can be identified that may have given rise to this trend. First, new nosographies and diagnostic criteria were introduced in 1992 with International Classification of Diseases, 10th Revision,\textsuperscript{58} and in 1994 with DSM-IV,\textsuperscript{1} that broadened the category of PDD. The most obvious example is the introduction of the entirely new category of Asperger syndrome in both diagnostic schemes, a diagnosis that did not exist previously. The direct impact of using different diagnostic criteria on prevalence estimates has been well illustrated in a Finish study\textsuperscript{59} where a twofold to threefold increase in prevalence resulted from applying old or new diagnostic criteria to the same survey data and subjects. Second, more expertise in diagnosing autism developed in the area with the establishment in recent years of a strong autism spectrum disorder clinical program at the Montreal Children's Hospital, the tertiary pediatric care institution that delivers services to Anglophone children. Third, a policy change at the MEQ level occurred in the summer of 2000 wherein the special education code 50 (PDD, as per DSM-IV) replaced the code 51 (autism, as per Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition) that had been in place for about a decade to identify PDD children with special needs and to provide additional funding for the schools.\textsuperscript{60} This change made the new special education code pertaining to children with autism broader and applicable to a greater number of children, especially those diagnosed with either Asperger syndrome or PDDNOS who subsequently became eligible for extra support. Fourth, in 2000, because of initiatives related to autism already underway in the board, the LBPSB received the Center of Excellence for Autism recognition from the MEQ. This afforded the board the opportunity to further develop their expertise in diagnosis, treatment, and inclusion of students with PDDs, as well as required it to be a resource to the other Anglophone boards in the province. Combined altogether, these factors account most certainly for the upward trend in diagnoses in successive birth cohorts, although it is not possible to definitely rule out other explanations.\textsuperscript{7} It is of interest that similar factors (broadening of diagnostic criteria and changes in policy with the 1990 revision of the Individuals with Disabilities Educational Act) have been hypothesized by several authors to explain upward trends in rates of PDDs in recent US studies.\textsuperscript{13–15,61,62} With rates of 0.6% to 0.7%, PDDs are among the most prevalent conditions impairing young children's lives, translating to >50,000 Canadian children below age 20 years in need of services.

Except for the authors' closing statement, “With rates of 0.6% to 0.7%, PDDs are among the most prevalent conditions impairing young children's lives, translating to >50,000 Canadian children below age 20 years in need of services,” the authors need to significantly revise their remarks because it is clear (from the “minimally” biased PDD data [in Grade 10 through Grade 1]) that the PDD incidence in children born in or after 1996 (most of the children in grades 2 and 1) clearly decreased from the highs seen in those children born before 1996 in 1993, 1994, and 1995 when Thimerosal exposure was at its peak in Canada.

“Thimerosal and Ethylmercury Exposure
During the 12 years encompassed by our study, thimerosal exposure before age 2 of each birth cohort changed several times and ranged from nil to a high value of 225 µg.”

Based on the Thimerosal-preserved hepatitis B (given from birth) and influenza vaccines that, though they were given to children in the 1990s, the authors neglected to address, the maximum level of mercury exposure from Thimerosal-preserved vaccines given to children 2-years old and younger probably ranged from < 100 µg to < 300 µg in the period covered by the author’s studies.

“This provided a unique opportunity to test the relationship of ethylmercury exposure with rates of PDDs, free of a known problem of vaccine safety studies when high rates of exposure in populations, and therefore low variability in exposure, constrain the data and limit the opportunity to detect effects.”
No association between thimerosal levels treated either continuously or categorically with PDD rates could be found in our study. In fact, it was remarkable that the PDD rates were at their highest value in birth cohorts that were thimerosal free, providing a clear and convincing message on the lack of an association. The results were robust and held true when various analyses were conducted to evaluate the potential impact of misclassification on exposure and diagnosis. Within each period of medium, high, or nil exposure, the same trend toward a steady increase in PDD rate was observed, demonstrating total independence of the 2 variables. Our results are entirely consistent with cohort,\textsuperscript{30–33} case-control,\textsuperscript{64} and other ecological studies performed in Denmark and Sweden.\textsuperscript{34,35} It is worth emphasizing 3 particular features of our results. First, because we were aware of limitations of ecological data, we performed complementary analyses on the subsample of Quebec-born subjects, a group with a very high probability of having been individually exposed to the official vaccination schedule of their birth cohort. The results remained unchanged. Second, the PDD rate in our study was high and consistent with recent epidemiological estimates coming from the United States\textsuperscript{65} and the United Kingdom.\textsuperscript{9} Thus, the convergence of our findings with those of the 2 ecological studies from Scandinavian countries\textsuperscript{34,35} suggests that the lack of association reported by these authors was not because of the lower prevalence of PDDs reported in their respective investigations. Third, exposure to ethylmercury in some birth cohorts of our study reached levels as high as those that were attained in the US immunization schedule in the 1990s and were higher than those ever reached in the United Kingdom and Scandinavian populations. Thus, the lack of association between PDD rate and high thimerosal exposure found in our study provides new evidence on the absence of an association between autism/PDD and high exposure levels to ethylmercury that is relevant to the North American public.”

Since the “unbiased” data reported by the authors in Grade 10 through Grade 1 clearly show a relation between maximum Thimerosal level and PDD incidence by grade cohort, the authors’ remarks here should be ignored because they are based on a false premise.

“MMR and Autism

During the 11-year interval encompassed in our study, rates of PDD significantly increased, whereas MMR vaccine uptake showed a slight opposite trend. This finding is consistent with several other ecological studies that have tested an association between MMR vaccine uptake and rates of autism or PDD in the United Kingdom,\textsuperscript{21,23} in Japan,\textsuperscript{66} in Sweden,\textsuperscript{67} and in the United States.\textsuperscript{22} In this study, we were able to restrict the analysis to Quebec-born subjects who were most certainly individually exposed to MMR in light of the very high MMR uptake in Quebec throughout the period (93%). Thus, the usual limitations of ecological studies because of lack of information on individual exposure might not have applied to our study. It is also noteworthy that the MMR vaccine uptake actually declined in the study period, whereas the rates of PDD went up, both trends being significant. The opposite directions of both trends make it even less likely that a true association was not detected in our data. This, too, makes it less plausible that a positive association applying only to a small subset of PDD children would have gone unnoticed. Moreover, the change in the MMR schedule of immunization with the introduction of a second dose by the age of 18 months occurring in 1996 gave us opportunities to examine the effects of a 2-dose MMR schedule in infants. First, we established that the lack of association between MMR uptake and PPD rates applied to the period (1987–1995) where a single MMR dose was administered at 12 months of age. Thus, rates of PDD were rapidly increasing well before the introduction of the 2-dose schedule and, during that first phase, the increase of PDD rate bore no relationship with MMR vaccine uptake. Second, we tested whether the introduction of a second MMR dose after 1995 accelerated the increase in PDD rates in the following 3 years. No statistically significant difference could be found between the rate of increase in PDD prevalence between the 1-dosing and the 2-dosing periods. In fact,
the end point prevalence estimate for 1998 was consistent with the value predicted on the basis of the 1987–1995 rate of increase. Therefore, 1 conclusion of this study is that 2-dosing schedule with MMR before age 2 is not associated with an increased risk of PDD.”

As this reviewer has previously established, the authors cannot, from this data, make any valid assertions about the effect of MMR vaccination on the observed PDD rates because it is confounded by the significant nearly concomitant decrease in the level of maximum Thimerosal exposure.

Based on this reality, the authors’ remarks here should simply be ignored.

“Limitations
Several limitations of our study must be acknowledged. First, we relied on administrative codes for the diagnosis of PDDs, and children could not be individually assessed for diagnostic confirmation. Nevertheless, the majority of children attending this school board with a PDD diagnosis were diagnosed in the tertiary medical center where one of us (E.F.) leads a specialized assessment team, and, therefore, the diagnostic assessment of this sample should be viewed with confidence in many cases. Also, results remained unchanged when we restricted the analyses to subjects with a stricter diagnosis of autistic disorder, a subsample where diagnostic misclassification is unlikely to be occurring. Second, the study cannot control for whether or not the high number of children with PDDs identified in this survey reflects migrations into the schools from this particular school board that are known to have a proactive policy of integration and support of children with PDDs. If families of preschoolers were to change residence to access the schools within the LBPSB for their child's education, this might inflate the number of children with PDD in this school board. To test this hypothesis, data from other school boards should be obtained, and knowledge of the residence of the family at birth and before school entry could also help to address this issue. Unfortunately, this information was not available in the survey data that we could obtain. However, it is worth noting that if such migrations occurred, it might bias our prevalence estimates but would have no impact on the thimerosal and MMR analyses, because migration into the area must be independent of vaccination history. Third, data about regression in the course of the development of children with PDD were not available in this study, precluding us from assessing risk associations with immunizations specifically for this subgroup. Nevertheless, the claim that only this PDD subtype would be sensitive to thimerosal exposure cannot be supported, because a significant increase of PDDs continued in Montreal after total discontinuation of thimerosal, providing strong evidence that thimerosal does not increase the risk of PDD and, indeed, of any PDD variant. If thimerosal exposure was associated with an increase in the risk of the regressive subtype of autism (thought to apply to 20% of PDD cases\textsuperscript{24,68}), then, at the very least, a slowing down in the upward trend in PDD rates should have been observed after 1996 when thimerosal was entirely removed from vaccine preparations. This was not observed, and the upward trend continued in a linear fashion. Rates of PDDs were, in fact, higher in the thimerosal-free birth cohorts than in any preceding period where exposure to thimerosal was at either medium or high levels. With respect to MMR, the claim of a putative "autistic enterocolitis" regressive phenotype has already failed to be supported in other studies,\textsuperscript{24,69} and epidemiological studies have shown that the regressive phenotype of autism has not increased over time.\textsuperscript{24,69,70} Given this, our findings of a regular increase in PDD and autistic disorder prevalence while MMR vaccine uptake was decreasing during the study period are not consistent with any increase in the risk of PDD, regressive or not, that could be attributed to MMR.”

In general, for the reasons stated in this reviewer’s previous in-depth commentary, most of the authors’ remarks here should also simply be ignored.
Implications
There are several important implications of this study. First, our study adds additional evidence deriving from a large, population-based survey that PDDs are one of the most common developmental disorders in young children. With a prevalence of 0.6% to 0.7%, the service implications are straightforward. Second, as in other recent studies, factors such as broadening of diagnostic criteria, improved awareness about the disorder, changes in official social and educational policies, and improved access to services are certainly the primary driving force underlying the increasing prevalence figures. Yet, the possibility that a real change in the incidence could have occurred as well cannot be definitely ruled out from existing data. Third, our findings clearly failed to detect any relationship between thimerosal exposure and rates of PDDs. These findings concur with those from other similar ecological investigations and of more controlled epidemiological studies. Previous negative studies, especially those conducted in European countries, have sometimes been criticized on the account that either the rates of PDDs were not as high as those in North America, that the cumulative exposure to thimerosal was much lower than that attained in the United States in the 1990s, or both. This study avoids both pitfalls and is, therefore, very informative for the North American public. In addition, the rate of exposure varied from nil to very high levels of vaccine-derived ethylmercury, allowing us to test for effects along the full range of exposure and to detect possible threshold effects as well. All of the results were negative. Fourth, as in previous studies, no effect of MMR vaccine could be detected on the risk of PDD. The trends went in opposite directions, making it unlikely that even small effects applying to a small subset of children would exist. Furthermore, this study added new evidence suggesting that the 2-MMR dose schedule before age 2 years also had no impact on rates of PDD. Fifth, parents of children with PDD and the general public should be made aware of the consistency of negative studies on the 2 hypotheses linking risk of autism and immunizations. Children with autism and their younger unaffected siblings should be vaccinated. Unvaccinated children are at much higher risk of contracting measles and suffering from its sometimes severe or lethal complications. There is no evidence for an epidemiological association between ethylmercury and autism and no scientific basis for using chelation therapies, which can be dangerous. Decreasing MMR uptake in the British isles has led to more frequent measles outbreaks of greater magnitude and to children’s deaths. Findings of negative studies are, indeed, more difficult to convey, but, here, the evidence lies in the striking convergence of studies accumulated by different groups, with different designs and in different places.”

Since the minimally biased data for Grade 10 through Grade 1 clearly support a link between PDD incidence and Thimerosal exposure level, the authors’ statements concerning the lack of a link between maximum organic mercury exposure from Thimerosal-preserved biological products and PDD incidence should be ignored.

Moreover, because of the confounding between increased MMR dosing (2 doses) and decreased Thimerosal-derived organic mercury exposure by age 2 (< 100 µg) as compared to the baseline 1 MMR dose and, on average, > 150 µg Thimerosal-derived organic mercury exposure by age 2, this data cannot be expected to shed much, if any, light on the relationship between PDD incidence and the number of MMR vaccine doses in the presence of the direct and indirect (in utero) exposure to Thimerosal-containing biological products, including Thimerosal-preserved vaccines and gammaglobulins.

To conduct a valid “worst case” study, the authors would have needed to conduct a double blind study of a population of not less than about 60,000 children who all received a significant Thimerosal dose (> 150 µg by age 2) and, at random, 1/3rd were given two placebo injections (1 at 12 months and 1 at 18 months of age), 1/3rd were a MMR at 12 months and a placebo at 18 months and the last third received 2 MMR
doses (1 at 12 months and the other at 18 months) with all other non-Thimerosal-preserved vaccines postponed until the child was at least 59 months of age.

Based on the children studied and their putative vaccination exposures, the authors’ indirect studies could not, for the reasons stated, be expected to shed any scientifically sound light on the link between the MMR vaccine and PDDs.

“ACKNOWLEDGMENTS

Dr. Fombonne's salary support is partially funded through the Canada Research Chair Canadian Institutes for Health Research (to Dr. Fombonne and McGill University).

We are indebted to Dr. Monique Landry from the Direction Générale de la Santé Publique of Montreal, Ministère de la Santé et des Services Sociaux, for her assistance in obtaining precise data on the immunization schedules in Quebec and to Nicole Boulianne de la Direction de Santé Publique de la Capitale Nationale for providing data on MMR uptake surveys.”

This reviewer has received no funds from any source to conduct this assessment of the study and results reported here.

However, this reviewer is indebted to Dr. Mark R. Geier, David A Geier, and Dr. Gary S. Goldman for their advice in how to proceed with the query for the minimum unpublished data required to evaluate the basic results reported, the confounding factors in the grade data that needed to be considered, and a review of the initial draft of this in-depth critical assessment of the authors’ paper.

“FOOTNOTES

Accepted Feb 15, 2006.

Address correspondence to Eric Fombonne, MD, Montréal Children's Hospital, 4018 Ste-Catherine West, Montreal, Quebec, Canada H3Z 1P2. E-mail: eric.fombonne@mcgill.ca”

[Note: Dr. Eric Fombonne, Director of Child Psychiatry for MUHC, Montreal Children's Hospital Psychiatry, Department of, Telephone: 1-514-412-4449 loc. 22174]

“In the United Kingdom, Dr Fombonne has provided advice on the epidemiology and clinical aspects of autism to scientists advising parents, to vaccine manufacturers, and to several government committees between 1998 and 2001. Since June 2004, Dr Fombonne has been an expert witness for vaccine manufacturers in US thimerosal litigation. None of his research has ever been funded by the industry.”

Please address correspondence to Paul G. King, PhD, 33 Hoffman Avenue, Lake Hiawatha, NJ 07034-1922 USA. Email: drking@gti.net.

In the United States and The Peoples Republic of China, Dr. King has long provided compensated and, in some cases, pro bono, advice on chemistry, pharmaceutics, and regulatory compliance as well as, when requested, providing consulting and training to pharmaceutical companies as well as at cost training and pro bono advice to the US FDA in the areas of representative sampling, compound purity assessment, specific identity assessment, sample and population statistics, quality systems, and CGMP compliance minimums.

From the United States, Dr. King has provided in-depth assessments of papers addressing the causeless “autism” disorder and other “causeless” neurodevelopmental, psychological disorders, the effectiveness and safety of vaccines and other biological
products containing Thimerosal, and the subacute mercury poisoning of humans and animals.

Since 1999, Dr. King has been engaged in the study of the published research in which some form of mercury may be a key factor in the papers that have directly or indirectly assessed the effects of mercury or its inorganic or organic compounds on humans, animals, cells and fundamental biochemical processes.

In addition, he has commented on many FDA guidances, is the lead author of the Citizen Petition filed with the FDA in docket 2004P-0349, has drafted legislation for the removal of all mercury-containing drugs from the market and the banning of the use of mercury in medical and dental procedures, has provided chain-of-custody protocols for use in the controlled testing of Thimerosal-containing drug products, written legislation designed to return the FDA to an effective agency whose only mission is to protect the public, and generated detailed legislation designed to truly improve the National Vaccine Injury Compensation Program.

None of these activities have been funded by any part of the healthcare establishment or by any activist, governmental, or public-interest group.

“TABLES:

**TABLE 1** Gender and Age Distribution by PDD Diagnostic Subtypes

<table>
<thead>
<tr>
<th>Variable</th>
<th>Autism (N = 61), n (%)</th>
<th>PDDNOS (N = 91), n (%)</th>
<th>Asperger (N = 28), n (%)</th>
<th>All PDD (N = 180), n (%)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>51 (83.6)</td>
<td>79 (86.8)</td>
<td>19 (67.9)</td>
<td>149 (82.8)</td>
<td>.066</td>
</tr>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5–7</td>
<td>30 (49.2)</td>
<td>17 (18.7)</td>
<td>2 (7.1)</td>
<td>49 (27.2)</td>
<td></td>
</tr>
<tr>
<td>8–10</td>
<td>13 (21.3)</td>
<td>44 (48.4)</td>
<td>10 (35.7)</td>
<td>67 (37.2)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>11–13</td>
<td>10 (16.4)</td>
<td>21 (23.1)</td>
<td>7 (25.0)</td>
<td>38 (21.1)</td>
<td></td>
</tr>
<tr>
<td>≥14</td>
<td>8 (13.1)</td>
<td>9 (9.9)</td>
<td>9 (32.1)</td>
<td>26 (14.4)</td>
<td></td>
</tr>
</tbody>
</table>

* The subject with CDD has been included in the autism group.

* The numbers in brackets are this reviewer’s computed incidence rates per 10,000 students based on the text’s 27,749 registered students; autism value does not match authors’ reported value of 21.6.
“FIGURES:

FIGURE 1 MMR vaccine coverage and PDD rates over time.

[Note: The left-hand “Y-axis” label should have been “Incidence/10000” instead of “Prevalence/10000.”]

FIGURE 2 Birth cohort prevalence rates and ethylmercury exposure. Dotted lines take into account the additional ethylmercury exposure because of a mass vaccination campaign against meningitis (see text).

[Note: The left-hand “Y-axis” label should have been “Incidence/10000” instead of “Prevalence/10000” and “FIGURE 2” legend “Birth cohort prevalence ...” should be “Birth cohort” incidence ....”]
REFERENCES


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FROM THE PEN OF PAUL G. KING


52. Landry M, Valiquette L, Allard R, Cioni M, Chrétien S. Enquête sur la couverture vaccinale des enfants de 24–30 mois. DSC Cité de la Santé de Laval et DSC Maisonneuve-Rosemont; Presented at: the 3rd Quebec Colloquium of Infectious Disease; Quebec, Canada; November 1992
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A. General Environmental, Elemental and Inorganic Mercury Toxicity Articles:

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B. General Organic Mercury Toxicity Articles:


C. Alkylmercury Compounds and General Toxicity Articles (for methylmercury and ethylmercury derivatives including Thimerosal [Thiomersal; Merthiolate]):


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73. Fagan DG, Pritchard JS, Clarkson TW, Greenwood MR. Organ mercury levels in infants with omphaloceles treated with organic mercurial antiseptic,” Archives of Disease in Childhood. 1977; 52: 962-964. [Also in the 2001 FDA TOX REPORT.]

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110. Engley FB, Jr. Mercurials as disinfectants. Evaluation of mercurial antimicrobial action and comparative toxicity. Soap and Chemical Specialties. 1956 Dec.: 200, 201, 203, 205, 223, 224 and 225. [This was an excellent article that was fashioned from a presentation at the Chemical Specialties Manufacturing Association Meeting by Dr. Frank Engley, Jr. earlier in 1956.]


D. Alkylmercury Immune-Related Articles (Methylmercury and Ethylmercury Derivatives Including Thimerosal):


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15. van't Veen AJ, van Joost T. Sensitization to Thimerosal (Merthiolate) is still present today. *Contact Dermatitis*. 1994; 31: 293-298. [From the 2001 FDA TOX REPORT.]


E. Alkylmercury Articles Addressing Issues Other Than Toxicity and Immune-System Dysfunction (e.g., human exposure, distribution in animal systems, epidemiological issues, testing, and autism):

1. Burbacher TM, Shen DD, Liberato N, Grant KS, Cernichiari E, and Clarkson T. Comparison of blood and brain mercury levels in infant monkeys exposed to
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methylmercury or vaccines containing Thimerosal. *Environ Health Perspec.* 2005; 113: 1015-1021. [DISTRIBUTION in developing monkeys.]

1.1 Based on the published work of Burbacher et al (Thomas M. Burbacher, Danny D. Shen, Noelle Liberato, Kimberly S. Grant, Elsa Cernichiari, and Thomas Clarkson, “Comparison of Blood and Brain Mercury Levels in Infant Monkeys Exposed to Methylmercury or Vaccines Containing Thimerosal,”* Environ Health Perspect* 113, pages 1015-1021 (2005)), if anything, Thimerosal is significantly more than twice as toxic, long-term, as “methyl mercury” ingested in the form of methylmercuric hydroxide in the Burbacher study.


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25. Pichichero ME, Cernichiari E, Lopreiato J, Treanor J. Mercury concentrations and metabolism in infants receiving vaccines containing thimerosal: A descriptive study. *Lancet*. 2002 Nov 30; 360: 1737-1741. [DESCRIBING mercury concentration and metabolism in infants – but study flawed because no mass balance studies were done to ensure mercury was cleared and not accumulating – only uncoordinated blood, stool and urine samples. Moreover, blood samples not taken for 3 days or more when putative half-life of 4 – 10 days (95% CI; 99.5% CI 1 – 13 days; avg. 7 days) so peak blood levels were missed increasing uncertainty in blood-clearance half-life values.]

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37. According to the web page http://cerhr.niehs.nih.gov/CERHRchems/index.html, contains Thimerosal, CAS 54-64-8, was not nominated by the FDA to have its toxicity appropriately studied until “11/99.” However, that proposed study’s status was changed to “Nomination Deferred” in “7/00” because there were “Chemicals with higher priorities” for, given the studies that were allowed to proceed, no scientifically sound reason. Last successfully accessed in December 2005; page no longer available to the public as of July 2006. [PROPOSED in-depth toxicity assessment.]


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45. Halsey NA. *Perspective on the use of thimerosal-containing vaccines*. Presentation at the National Vaccine Advisory Committee Workshop on Thimerosal and Vaccines, August 11-12, 1999. Institute of Vaccine Safety website. [VACCINE issues.]


52. No authors listed. From the Centers for Disease Control and Prevention. *Recommendations regarding the use of vaccines that contain thimerosal as a preservative*. *JAMA*. 1999 Dec 8; 282(22): 2114-2115.


54. FDA estimated Thimerosal used as a preservative in more than 30 biological products in report in *Federal Register*. 1999 Nov 19; 64: 63323-63324. [THIMEROSAL in > 30 biological products as a preservative; from the 2001 FDA TOX REPORT.]


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45(2): 158-163. [SEROTONIN & beta-ENDORPHIN in autistics & their 1st degree relatives.]

58. Egan WM. Thimerosal in Vaccines. Presentation to the FDA, September 14, 1999. [VACCINE issues.]


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86. Aschner M, Mullaney KJ, Wagoner D, Lash LH, Kimelberg HK. Intracellular glutathione (GSH) levels modulate mercuric chloride (MC)- and methylmercuric chloride (MeHgCl)-induced amino acid release from neonatal rat primary astrocytes cultures. *Brain Res*. 1994; 664(1-2); 133-140. [GLUTATHIONE LEVELS modulated by mercury compounds in autism.]

87. Moller H. All these positive tests to thimerosal. *Contact Dermatitis*. 1994; 31:209-213. [ALLERGY to Thimerosal; from the 2001 FDA TOX REPORT.]


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97. Undated, 7-page 1991 Merck memo: From: “Maurice R. Hilleman WP 26-200B”; To: “DR. DAVID GORDON RY 33-76”; Regarding: “VACCINE TASKFORCE ASSIGNMENT THIMEROSAL (MERTHIOLATE) PRESERVATIVE – PROBLEMS, ANALYSIS, SUGGESTIONS FOR RESOLUTION,” which: a) was discovered in a recent court case and b) clearly indicates that Merck had been aware of the excessive level of mercury being injected into babies for some time and had discussed the issue with the FDA’s CBER division (who reportedly was ‘unconcerned”). This memo ends with the following two telling paragraphs in the postscript:

“The seasoned conclusion Wigzell gives is, “Our opinion, however, is that the problems associated with the spread of mercury via vaccination are so minor that there is no reason to push a hastened solution.”

“Note, however, that Wigzell mentions only Thimerosal-reserved DTP or DT given in at least 3 doses since the 1950s. Even with such small exposures, Sweden is moving as expeditiously as feasible to achieve a zero input of mercury from Thimerosal.”


102. Cox NH, Forsyth A. Thimerosal allergy and vaccination reactions. Contact Dermatitis. 1988; 18: 229-233. [Vaccination reactions; also in the 2001 FDA TOX REPORT.]


104. Ritvo ER, Freeman BJ, Scheibel AB, Duong T, Robinson H, Guthrie D, Ritvo A. Lower Purkinje cell counts in the cerebella of four autistic subjects: initial findings of the
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110. FDA’s proposed limit for mercury from ingesting methylmercury-containing foods and other products was reported in the *Federal Register*. 1979 Jan 19; 44: 3990. [PROPOSED DAILY INTAKE LIMIT for mercury; from the 2001 FDA TOX REPORT.]


118. DEFINITIONS: a) According to the FDA’s 2000 definition, a “Trace Thimerosal” vaccine is any vaccine that nominally contains not more than 1 µg of Hg/ dose; b) a “Near-Trace Thimerosal” vaccine is any vaccine that nominally contains not more than 1.25 µg of Kg/0.5-mL dose (Dr. King’s working definition); and c) a “Thimerosal Preserved” vaccine is any vaccine that nominally contains not less than 8 µg of Hg/0.5-mL dose but not more than 25 µg of Hg/0.5 mL dose (in the US); in some other countries, e.g., Brazil, the upper limit for Thimerosal is reported to include 50 µg of Hg/0.5 mL dose (0.02% Thimerosal in vaccine formulation).

119. MMR-RELATED:
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120. INFLUENZA VACCINE STUDIES


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121. THIMEROSAL-RELATED PATENTS:


F. Pertinent MMR References:


G. Key Federal Statutes, Regulations, and Judicial Decisions:
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1. **21 CFR Section 610.15(a).** Thimerosal has been illegally used as a preservative since 1973 when the FDA enacted regulations requiring a compound to be proven safe before use as a preservative. (See: 21 CFR 610.15(a):

“TITLE 21--FOOD AND DRUGS.
CHAPTER I--FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH AND HUMAN SERVICES
PART 610--GENERAL BIOLOGICAL PRODUCTS STANDARDS
Subpart B--General Provisions
Sec. 610.15  Constituent materials.
(a) Ingredients, preservatives, diluents, adjuvants. All ingredients used in a licensed product, and any diluent provided as an aid in the administration of the product, shall meet generally accepted standards of purity and quality. Any preservative used shall be sufficiently nontoxic so that the amount present in the recommended dose of the product will not be toxic to the recipient, and in the combination used it shall not denature the specific substances in the product to result in a decrease below the minimum acceptable potency within the dating period when stored at the recommended temperature. …”

[Note: The crude toxicity studies done under contract to the FDA, in the 1960s, did not establish a safe level for exposure in humans. In addition, it did not even study: a) the effects of long-term intermittent dosing at drug levels, b) the dosing in pregnancy (including multi-generation reproduction studies), c) dosing in developing infants, children and adolescents, or d) dosing in the elderly. The animal studies that were conducted only looked for gross changes in one animal species (the rat) without any proof of comparable toxicity in humans. Since other studies had been published that had established Thimerosal is a teratogen and mutagen as well as causes multigenerational genetic effects, the failure to do these studies cannot be justified. Finally, the FDA’s 2001 literature studies failed to find many important references including those published by governmental agencies including the FDA.]


“(B) if it is a drug and the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice to assure that such drug meets the requirements of this chapter as to safety and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess;”

after the existing 21 U.S.C. Section 351(2), which was redesignated as 21 U.S.C. Section 351(2)(A).

3. **21 U.S.C. Section 321. Definitions; generally.**— Especially:
   a. **Sec. 321(g)(1):** “The term ‘drug’ means (A) articles recognized in the official United States Pharmacopoeia, official Homeopathic Pharmacopoeia of the United States, or official National Formulary, or any supplement to any of them; and (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and (C) articles (other than food) intended to affect the structure or any function of the body of man or other animals; and (D) articles intended for use as a component of any article specified in clause (A), (B), or (C). A food or dietary supplement for which a claim, subject to sections 343(r)(1)(B) and 343(r)(3) of this title or sections 343(r)(1)(B) and 343(r)(5)(D) of this title, is made in accordance with the requirements of section 343(r) of this title is not a drug solely because the label or the labeling contains such a claim. A food, dietary ingredient, or dietary supplement for which a truthful and not misleading statement is made in accordance with section 343(r)(6) of this title is not a drug under clause (C) solely because the label or the labeling contains such a statement.”
   b. **Sec. 321(u):** “The term ‘safe’ as used in paragraph(s) of this section and in sections 348, 360b, and 379e of this title, has reference to the health of man or animal.”
   c. **Sec. 321(bb):** “The term ‘knowingly’ or ‘knew’ means that a person, with respect to information · (1) has actual knowledge of the information, or (2) acts in deliberate ignorance or reckless disregard of the truth or falsity of the information.”
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d. **Sec. 321(cc):** “For purposes of section 335a of this title, the term ‘high managerial agent’ - (1) means -
(A) an officer or director of a corporation or an association, (B) a partner of a partnership, or (C) any
employee or other agent of a corporation, association, or partnership, having duties such that the conduct
of such officer, director, partner, employee, or agent may fairly be assumed to represent the policy of the
corporation, association, or partnership, and (2) includes persons having management responsibility for
(A) submissions to the Food and Drug Administration regarding the development or approval of any drug
product, (B) production, quality assurance, or quality control of any drug product, or (C) research and
development of any drug product.”

e. **Sec. 321(dd):** “For purposes of sections 335a and 335b of this title, the term ‘drug product’ means a
drug subject to regulation under section 355, 360b, or 382 of this title or under section 262 of title 42.”

4. **21 U.S.C. Section 331. Prohibited acts.** “The following acts and the causing thereof are prohibited:
(a) The introduction or delivery for introduction into interstate commerce of any food, drug, device, or
cosmetic that is adulterated or misbranded.
(b) The adulteration or misbranding of any food, drug, device, or cosmetic in interstate commerce.
(c) The receipt in interstate commerce of any food, drug, device, or cosmetic that is adulterated or
misbranded, and the delivery or proffered delivery thereof for pay or otherwise.
(d) The introduction or delivery for introduction into interstate commerce of any article in violation of section
344, 355, or 360b-3 of this title.
(e) The refusal to permit access to or copying of any record as required by section 350a, 350c, 354, 360b-3,
373, or 374 of this title: or the failure to establish or maintain any record, or make any report, required
under section 350a, 350c, 354, 355(i) or (k), 360b(a)(4)(C), 360b(j), (l), or (m), 360e(f), 360i, or 360b-3
of this title, or the refusal to permit access to or verification or copying of any such required record.
(f) The refusal to permit entry or inspection as authorized by section 374 of this title.
(g) The manufacture within any Territory of any food, drug, device, or cosmetic that is adulterated or
misbranded.
(h) The giving of a guaranty or undertaking referred to in section 333(c)(2) of this title, which guaranty or
undertaking is false, except by a person who relied upon a guaranty or undertaking to the same effect signed
by, and containing the name and address of, the person residing in the United States from whom he received in
good faith the food, drug, device, or cosmetic; or the giving of a guaranty or undertaking referred to in section
333(c)(3) of this title, which guaranty or undertaking is false.
(i) ..... 
(j) ..... 
(k) ..... 
(m) ..... 
(n) ..... 
(o) In the case of a prescription drug distributed or offered for sale in interstate commerce, the failure of the
manufacturer, packer, or distributor thereof to maintain for transmittal, or to transmit, to any practitioner
licensed by applicable State law to administer such drug who makes written request for information as to such
drug, true and correct copies of all printed matter which is required to be included in any package in which that
drug is distributed or sold, or such other printed matter as is approved by the Secretary. Nothing in this
paragraph shall be construed to exempt any person from any labeling requirement imposed by or under other
provisions of this chapter.
(p) ..... 
(q) (1) ..... 
(2) ..... 
(r) ..... 
(s) The failure to provide the notice required by section 350a(c) or 350a(e) of this title, the failure to make the
reports required by section 350a(f)(1)(B) of this title, the failure to retain the records required by section
350a(b)(4) of this title, or the failure to meet the requirements prescribed under section 350a(f)(3) of this title.
(t) ..... 
(u) ..... 
(v) .....
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(w) The making of a knowingly false statement in any statement, certificate of analysis, record, or report required or requested under section 381(d)(3) of this title; the failure to submit a certificate of analysis as required under such section; the failure to maintain records or to submit records or reports as required by such section; the release into interstate commerce of any article or portion thereof imported into the United States under such section or any finished product made from such article or portion, except for export in accordance with section 381(e) or 382 of this title, or with section 262(h) of title 42; or the failure to so export or to destroy such an article or portions thereof, or such a finished product.

(x) ….

(y) In the case of a drug, device, or food:

(1) the submission of a report or recommendation by a person accredited under section 360m of this title that is false or misleading in any material respect;

(2) the disclosure by a person accredited under section 360m of this title of confidential commercial information or any trade secret without the express written consent of the person who submitted such information or secret to such person; or

(3) the receipt by a person accredited under section 360m of this title of a bribe in any form or the doing of any corrupt act by such person associated with a responsibility delegated to such person under this chapter.

(z) ….

(aa) ….

(bb) ….

(cc) ….

(dd) ….

(ee) ….

(ff) ….

(gg) The knowing failure of a person accredited under paragraph (2) of section 374(g) of this title to comply with paragraph (7)(E) of such section; the knowing inclusion by such a person of false information in an inspection report under paragraph (7)(A) of such section; or the knowing failure of such a person to include material facts in such a report.


"(a) Violation of section 331 of this title; second violation; intent to defraud or mislead

(1) Any person who violates a provision of section 331 of this title shall be imprisoned for not more than one year or fined not more than $1,000, or both.

(2) Notwithstanding the provisions of paragraph (1) of this section, if any person commits such a violation after a conviction of him under this section has become final, or commits such a violation with the intent to defraud or mislead, such person shall be imprisoned for not more than three years or fined not more than $10,000, or both.

(b) Prescription drug marketing violations

(1) Notwithstanding subsection (a) of this section, any person who violates section 331(t) of this title by:

(A) knowingly importing a drug in violation of section 381(d)(1) of this title, (B) knowingly selling, purchasing, or trading a drug or drug sample or knowingly offering to sell, purchase, or trade a drug or drug sample, in violation of section 353(c)(1) of this title, (C) knowingly selling, purchasing, or trading a coupon, knowingly offering to sell, purchase, or trade such a coupon, or knowingly counterfeiting such a coupon, in violation of section 353(c)(2) of this title, or (D) knowingly distributing drugs in violation of section 353(e)(2)(A) of this title, shall be imprisoned for not more than 10 years or fined not more than $250,000, or both.

(2) Any manufacturer or distributor who distributes drug samples by means other than the mail or common carrier whose representative, during the course of the representative’s employment or association with that manufacturer or distributor, violated section 331(t) of this title because of a violation of section 353(c)(1) of this title or violated any State law prohibiting the sale, purchase, or trade of a drug sample subject to section 353(b) of this title or the offer to sell, purchase, or trade such a drug sample shall, upon conviction of the representative for such violation, be subject to the following civil penalties: (A) A civil penalty of not more than $50,000 for each of the first two such violations resulting in a conviction of any representative of the manufacturer or distributor in any 10-year period. (B) A civil penalty of not more than $1,000,000 for each violation resulting in a conviction of any representative after the second conviction in any 10-year period.
For the purposes of this paragraph, multiple convictions of one or more persons arising out of the same event or transaction, or a related series of events or transactions, shall be considered as one violation.

(3) Any manufacturer or distributor who violates section 331(t) of this title because of a failure to make a report required by section 353(d)(3)(E) of this title shall be subject to a civil penalty of not more than $100,000.

(4) (A) If a manufacturer or distributor or any representative of such manufacturer or distributor provides information leading to the institution of a criminal proceeding against, and conviction of, any representative of that manufacturer or distributor for a violation of section 331(t) of this title because of a sale, purchase, or trade or offer to purchase, sell, or trade a drug sample in violation of section 353(c)(1) of this title or for a violation of State law prohibiting the sale, purchase, or trade or offer to sell, purchase, or trade a drug sample, the conviction of such representative shall not be considered as a violation for purposes of paragraph (2).

(B) If, in an action brought under paragraph (2) against a manufacturer or distributor relating to the conviction of a representative of such manufacturer or distributor for the sale, purchase, or trade of a drug or the offer to sell, purchase, or trade a drug, it is shown, by clear and convincing evidence-

(i) that the manufacturer or distributor conducted, before the institution of a criminal proceeding against such representative for the violation which resulted in such conviction, an investigation of events or transactions which would have led to the reporting of information leading to the institution of a criminal proceeding against, and conviction of, such representative for such purchase, sale, or trade or offer to purchase, sell, or trade, or

(ii) that, except in the case of the conviction of a representative employed in a supervisory function, despite diligent implementation by the manufacturer or distributor of an independent audit and security system designed to detect such a violation, the manufacturer or distributor could not reasonably have been expected to have detected such violation, the conviction of such representative shall not be considered as a conviction for purposes of paragraph (2).

(5) If a person provides information leading to the institution of a criminal proceeding against, and conviction of, a person for a violation of section 331(t) of this title because of the sale, purchase, or trade of a drug sample or the offer to sell, purchase, or trade a drug sample in violation of section 353(c)(1) of this title, such person shall be entitled to one-half of the criminal fine imposed and collected for such violation but not more than $125,000.

(6) Notwithstanding subsection (a) of this section, any person who is a manufacturer or importer of a prescription drug under section 384(b) of this title and knowingly fails to comply with a requirement of section 384(e) of this title that is applicable to such manufacturer or importer, respectively, shall be imprisoned for not more than 10 years or fined not more than $250,000, or both.

(c) Exceptions in certain cases of good faith, etc.

No person shall be subject to the penalties of subsection (a)(1) of this section, (1) for having received in interstate commerce any article and delivered it or proffered delivery of it, if such delivery or proffer was made in good faith, unless he refuses to furnish on request of an officer or employee duly designated by the Secretary the name and address of the person from whom he purchased or received such article and copies of all documents, if any there be, pertaining to the delivery of the article to him; or (2) for having violated section 331(a) or (d) of this title, if he establishes a guaranty or undertaking signed by, and containing the name and address of, the person residing in the United States from whom he received in good faith the article, to the effect, in case of an alleged violation of section 331(a) of this title, that such article is not adulterated or misbranded, within the meaning of this chapter designating this chapter or to the effect, in case of an alleged violation of section 331(d) of this title, that such article which may not, under the provisions of section 344 or 355 of this title, be introduced into interstate commerce; or (3) for having violated section 331(a) of this title, where the violation exists because the article is adulterated by reason of containing a color additive not from a batch certified in accordance with regulations promulgated by the Secretary under this chapter, if such person establishes a guaranty or undertaking signed by, and containing the name and address of, the manufacturer of the color additive, to the effect that such color additive was from a batch certified in accordance with the applicable regulations promulgated by the Secretary under this chapter; or (4) for having violated section 331(b), (c) or (k) of this title by failure to comply with section 352(f) of this title in respect to an article received in interstate commerce to which neither section 353(a) nor 353(b)(l) of this title is applicable, if
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the delivery or proffered delivery was made in good faith and the labeling at the time thereof contained the same directions for use and warning statements as were contained in the labeling at the time of such receipt of such article; or (5) for having violated section 331(j)(2) of this title if such person acted in good faith and had no reason to believe that use of the punch, die, plate, stone, or other thing involved would result in a drug being a counterfeit drug, or for having violated section 331(j)(3) of this title if the person doing the act or causing it to be done acted in good faith and had no reason to believe that the drug was a counterfeit drug.

(d) Exceptions involving misbranded food

(e) Prohibited distribution of human growth hormone

(1) Except as provided in paragraph (2), whoever knowingly distributes, or possesses with intent to distribute, human growth hormone for any use in humans other than the treatment of a disease or other recognized medical condition, where such use has been authorized by the Secretary of Health and Human Services under section 355 of this title and pursuant to the order of a physician, is guilty of an offense punishable by not more than 5 years in prison, such fines as are authorized by title 18, or both.

(2) Whoever commits any offense set forth in paragraph (1) and such offense involves an individual under 18 years of age is punishable by not more than 10 years imprisonment, such fines as are authorized by title 18, or both.

(3) Any conviction for a violation of paragraphs (1) and (2) of this subsection shall be considered a felony violation of the Controlled Substances Act [21 U.S.C. 801 et seq.] for the purposes of forfeiture under section 413 of such Act [21 U.S.C. 853].

(4) As used in this subsection the term “human growth hormone” means somatrem, somatropin, or an analogue of either of them.

(5) The Drug Enforcement Administration is authorized to investigate offenses punishable by this subsection.

(f) Redesignated (g)

(g) Violations related to devices

(!1) So in original. Words ‘of this section’ probably should not appear.”

6. 21 CFR PART 210—CURRENT GOOD MANUFACTURING PRACTICE IN MANUFACTURING, PROCESSING, PACKING, OR HOLDING OF DRUGS; GENERAL. —

Especially:

a. “§ 210.1 Status of current good manufacturing practice regulations.

(a) The regulations set forth in this part and in parts 211 through 226 of this chapter contain the minimum current good manufacturing practice for methods to be used in, and the facilities or controls to be used for, the manufacture, processing, packing, or holding of a drug to assure that such drug meets the requirements of the act as to safety, and has the identity and strength and meets the quality and purity characteristics that it purports or is represented to possess.

(b) The failure to comply with any regulation set forth in this part and in parts 211 through 226 of this chapter in the manufacture, processing, packing, or holding of a drug shall render such drug to be adulterated under section 501(a)(2)(B) of the act and such drug, as well as the person who is responsible for the failure to comply, shall be subject to regulatory action.

(c) Owners and operators of establishments engaged in the recovery, donor screening, testing (including donor testing), processing, storage, labeling, packaging, or distribution of human cells, tissues, and cellular and tissue-based products (HCT/Ps), as defined in §1271.3(d) of this chapter, that are drugs (subject to review under an application submitted under section 505 of the act or under a biological product license application under section 351 of the Public Health Service Act), are subject to the donor-eligibility and applicable current good tissue practice procedures set forth in part 1271 subparts C and D of this chapter, in addition to the regulations in this part and in parts 211 through 226 of this chapter. Failure to comply with any applicable regulation set forth in this part, in parts 211 through 226 of this chapter, in part 1271 subpart C of this chapter, or in part 1271 subpart D of this chapter with respect to the manufacture, processing, packing or holding of a drug, renders an HCT/P adulterated under section 501(a)(2)(B) of the act. Such HCT/P, as well as the person who is responsible for the failure to comply, is subject to regulatory action.”

b. “§ 210.2 Applicability of current good manufacturing practice regulations.
(a) The regulations in this part and in parts 211 through 226 of this chapter as they may pertain to a drug; in parts 600 through 680 of this chapter as they may pertain to a biological product for human use; and in part 1271 of this chapter as they are applicable to a human cell, tissue, or cellular or tissue-based product (HCT/P) that is a drug (subject to review under an application submitted under section 505 of the act or under a biological product license application under section 351 of the Public Health Service Act); shall be considered to supplement, not supersede, each other, unless the regulations explicitly provide otherwise. In the event of a conflict between applicable regulations in this part and in other parts of this chapter, the regulation specifically applicable to the drug product in question shall supersede the more general.

(b) If a person engages in only some operations subject to the regulations in this part, in parts 211 through 226 of this chapter, in parts 600 through 680 of this chapter, and in part 1271 of this chapter, and not in others, that person need only comply with those regulations applicable to the operations in which he or she is engaged.”

c. “§ 210.3 Definitions.
(a) The definitions and interpretations contained in section 201 of the act shall be applicable to such terms when used in this part and in parts 211 through 226 of this chapter.

(b) The following definitions of terms apply to this part and to parts 211 through 226 of this chapter.
   (2) Batch means a specific quantity of a drug or other material that is intended to have uniform character and quality, within specified limits, and is produced according to a single manufacturing order during the same cycle of manufacture.
   (3) Component means any ingredient intended for use in the manufacture of a drug product, including those that may not appear in such drug product.
   (4) Drug product means a finished dosage form, for example, tablet, capsule, solution, etc., that contains an active drug ingredient generally, but not necessarily, in association with inactive ingredients. The term also includes a finished dosage form that does not contain an active ingredient but is intended to be used as a placebo.
   (5) Fiber means any particulate contaminant with a length at least three times greater than its width.
   (6) Non-fiber-releasing filter means any filter, which after any appropriate pretreatment such as washing or flushing, will not release fibers into the component or drug product that is being filtered. All filters composed of asbestos are deemed to be fiber-releasing filters.
   (7) Active ingredient means any component that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of man or other animals. The term includes those components that may undergo chemical change in the manufacture of the drug product and be present in the drug product in a modified form intended to furnish the specified activity or effect.
   (8) Inactive ingredient means any component other than an active ingredient.
   (9) In-process material means any material fabricated, compounded, blended, or derived by chemical reaction that is produced for, and used in, the preparation of the drug product.
   (10) Lot means a batch, or a specific identified portion of a batch, having uniform character and quality within specified limits; or, in the case of a drug product produced by continuous process, it is a specific identified amount produced in a unit of time or quantity in a manner that assures its having uniform character and quality within specified limits.
   (11) Lot number, control number, or batch number means any distinctive combination of letters, numbers, or symbols, or any combination of them, from which the complete history of the manufacture, processing, packing, holding, and distribution of a batch or lot of drug product or other material can be determined.
   (12) Manufacture, processing, packing, or holding of a drug product includes packaging and labeling operations, testing, and quality control of drug products.
   (13) The term medicated feed means any Type B or Type C medicated feed as defined in §558.3 of this chapter. The feed contains one or more drugs as defined in section 201(g) of the act. The manufacture of medicated feeds is subject to the requirements of part 225 of this chapter.
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(14) The term medicated premix means a Type A medicated article as defined in §558.3 of this chapter. The article contains one or more drugs as defined in section 201(g) of the act. The manufacture of medicated premixes is subject to the requirements of part 226 of this chapter.

(15) Quality control unit means any person or organizational element designated by the firm to be responsible for the duties relating to quality control.

(16) Strength means:
   (i) The concentration of the drug substance (for example, weight/weight, weight/volume, or unit dose/volume basis), and/or
   (ii) The potency, that is, the therapeutic activity of the drug product as indicated by appropriate laboratory tests or by adequately developed and controlled clinical data (expressed, for example, in terms of units by reference to a standard).

(17) Theoretical yield means the quantity that would be produced at any appropriate phase of manufacture, processing, or packing of a particular drug product, based upon the quantity of components to be used, in the absence of any loss or error in actual production.

(18) Actual yield means the quantity that is actually produced at any appropriate phase of manufacture, processing, or packing of a particular drug product.

(19) Percentage of theoretical yield means the ratio of the actual yield (at any appropriate phase of manufacture, processing, or packing of a particular drug product) to the theoretical yield (at the same phase), stated as a percentage.

(20) Acceptance criteria means the product specifications and acceptance/rejection criteria, such as acceptable quality level and unacceptable quality level, with an associated sampling plan, that are necessary for making a decision to accept or reject a lot or batch (or any other convenient subgroups of manufactured units).

(21) Representative sample means a sample that consists of a number of units that are drawn based on rational criteria such as random sampling and intended to assure that the sample accurately portrays the material being sampled.

(22) Gang-printed labeling means labeling derived from a sheet of material on which more than one item of labeling is printed.

7. 21 CFR Part 211—CURRENT GOOD MANUFACTURING PRACTICE FOR FINISHED PHARMACEUTICALS.— Especially:


§ 211.1 Scope.

(a) The regulations in this part contain the minimum current good manufacturing practice for preparation of drug products for administration to humans or animals.

(b) The current good manufacturing practice regulations in this chapter as they pertain to drug products; in parts 600 through 680 of this chapter, as they pertain to drugs that are also biological products for human use; and in part 1271 of this chapter, as they are applicable to drugs that are also human cells, tissues, and cellular and tissue-based products (HCT/Ps) and that are drugs (subject to review under an application submitted under section 505 of the act or under a biological product license application under section 351 of the Public Health Service Act); supplement and do not supersede the regulations in this part unless the regulations explicitly provide otherwise. In the event of a conflict between applicable regulations in this part and in other parts of this chapter, or in parts 600 through 680 of this chapter, or in part 1271 of this chapter, the regulation specifically applicable to the drug product in question shall supersede the more general.

(c) Pending consideration of a proposed exemption, published in the Federal Register of September 29, 1978, the requirements in this part shall not be enforced for OTC drug products if the products and all their ingredients are ordinarily marketed and consumed as human foods, and which products may also fall within the legal definition of drugs by virtue of their intended use. Therefore, until further notice, regulations under part 110 of this chapter, and where applicable, parts 113 to 129 of this chapter, shall be applied in determining whether these OTC drug products that are also foods are manufactured, processed, packed, or held under current good manufacturing practice.

§ 211.3 Definitions.

The definitions set forth in §210.3 of this chapter apply in this part.”
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b. "Subpart B—Organization and Personnel

§ 211.22 Responsibilities of quality control unit.
(a) There shall be a quality control unit that shall have the responsibility and authority to approve or reject all components, drug product containers, closures, in-process materials, packaging material, labeling, and drug products, and the authority to review production records to assure that no errors have occurred or, if errors have occurred, that they have been fully investigated. The quality control unit shall be responsible for approving or rejecting drug products manufactured, processed, packed, or held under contract by another company.
(b) Adequate laboratory facilities for the testing and approval (or rejection) of components, drug product containers, closures, packaging materials, in-process materials, and drug products shall be available to the quality control unit.
(c) The quality control unit shall have the responsibility for approving or rejecting all procedures or specifications impacting on the identity, strength, quality, and purity of the drug product.
(d) The responsibilities and procedures applicable to the quality control unit shall be in writing; such written procedures shall be followed.

§ 211.25 Personnel qualifications.
(a) Each person engaged in the manufacture, processing, packing, or holding of a drug product shall have education, training, and experience, or any combination thereof, to enable that person to perform the assigned functions. Training shall be in the particular operations that the employee performs and in current good manufacturing practice (including the current good manufacturing practice regulations in this chapter and written procedures required by these regulations) as they relate to the employee's functions. Training in current good manufacturing practice shall be conducted by qualified individuals on a continuing basis and with sufficient frequency to assure that employees remain familiar with CGMP requirements applicable to them.
(b) Each person responsible for supervising the manufacture, processing, packing, or holding of a drug product shall have the education, training, and experience, or any combination thereof, to perform assigned functions in such a manner as to provide assurance that the drug product has the safety, identity, strength, quality, and purity that it purports or is represented to possess.
(c) There shall be an adequate number of qualified personnel to perform and supervise the manufacture, processing, packing, or holding of each drug product.

§ 211.28 Personnel responsibilities.
(a) Personnel engaged in the manufacture, processing, packing, or holding of a drug product shall wear clean clothing appropriate for the duties they perform. Protective apparel, such as head, face, hand, and arm coverings, shall be worn as necessary to protect drug products from contamination.
(b) Personnel shall practice good sanitation and health habits.
(c) Only personnel authorized by supervisory personnel shall enter those areas of the buildings and facilities designated as limited-access areas.
(d) Any person shown at any time (either by medical examination or supervisory observation) to have an apparent illness or open lesions that may adversely affect the safety or quality of drug products shall be excluded from direct contact with components, drug product containers, closures, in-process materials, and drug products until the condition is corrected or determined by competent medical personnel not to jeopardize the safety or quality of drug products. All personnel shall be instructed to report to supervisory personnel any health conditions that may have an adverse effect on drug products.

§ 211.34 Consultants.
Consultants advising on the manufacture, processing, packing, or holding of drug products shall have sufficient education, training, and experience, or any combination thereof, to advise on the subject for which they are retained. Records shall be maintained stating the name, address, and qualifications of any consultants and the type of service they provide."

c. "Subpart I—Laboratory Controls

§ 211.160 General requirements.
(a) The establishment of any specifications, standards, sampling plans, test procedures, or other laboratory control mechanisms required by this subpart, including any change in such specifications, standards,
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sampling plans, test procedures, or other laboratory control mechanisms, shall be drafted by the appropriate organizational unit and reviewed and approved by the quality control unit. The requirements in this subpart shall be followed and shall be documented at the time of performance. Any deviation from the written specifications, standards, sampling plans, test procedures, or other laboratory control mechanisms shall be recorded and justified.

(b) Laboratory controls shall include the establishment of scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that components, drug product containers, closures, in-process materials, labeling, and drug products conform to appropriate standards of identity, strength, quality, and purity. Laboratory controls shall include:

(1) Determination of conformance to appropriate written specifications for the acceptance of each lot within each shipment of components, drug product containers, closures, and labeling used in the manufacture, processing, packing, or holding of drug products. The specifications shall include a description of the sampling and testing procedures used. Samples shall be representative and adequately identified. Such procedures shall also require appropriate retesting of any component, drug product container, or closure that is subject to deterioration.

(2) Determination of conformance to written specifications and a description of sampling and testing procedures for in-process materials. Such samples shall be representative and properly identified.

(3) Determination of conformance to written descriptions of sampling procedures and appropriate specifications for drug products. Such samples shall be representative and properly identified.

(4) The calibration of instruments, apparatus, gauges, and recording devices at suitable intervals in accordance with an established written program containing specific directions, schedules, limits for accuracy and precision, and provisions for remedial action in the event accuracy and/or precision limits are not met. Instruments, apparatus, gauges, and recording devices not meeting established specifications shall not be used.

§ 211.165 Testing and release for distribution.
(a) For each batch of drug product, there shall be appropriate laboratory determination of satisfactory conformance to final specifications for the drug product, including the identity and strength of each active ingredient, prior to release. Where sterility and/or pyrogen testing are conducted on specific batches of short-lived radiopharmaceuticals, such batches may be released prior to completion of sterility and/or pyrogen testing, provided such testing is completed as soon as possible.

(b) There shall be appropriate laboratory testing, as necessary, of each batch of drug product required to be free of objectionable microorganisms.

(c) Any sampling and testing plans shall be described in written procedures that shall include the method of sampling and the number of units per batch to be tested; such written procedure shall be followed.

(d) Acceptance criteria for the sampling and testing conducted by the quality control unit shall be adequate to assure that batches of drug products meet each appropriate specification and appropriate statistical quality control criteria as a condition for their approval and release. The statistical quality control criteria shall include appropriate acceptance levels and/or appropriate rejection levels.

(e) The accuracy, sensitivity, specificity, and reproducibility of test methods employed by the firm shall be established and documented. Such validation and documentation may be accomplished in accordance with §211.194(a)(2).

(f) Drug products failing to meet established standards or specifications and any other relevant quality control criteria shall be rejected. Reprocessing may be performed. Prior to acceptance and use, reprocessed material must meet appropriate standards, specifications, and any other relevant criteria.

§ 211.166 Stability testing.
(a) There shall be a written testing program designed to assess the stability characteristics of drug products. The results of such stability testing shall be used in determining appropriate storage conditions and expiration dates. The written program shall be followed and shall include:

(1) Sample size and test intervals based on statistical criteria for each attribute examined to assure valid estimates of stability;

(2) Storage conditions for samples retained for testing;

(3) Reliable, meaningful, and specific test methods;
(4) Testing of the drug product in the same container-closure system as that in which the drug product is marketed;
(5) Testing of drug products for reconstitution at the time of dispensing (as directed in the labeling) as well as after they are reconstituted.

(b) An adequate number of batches of each drug product shall be tested to determine an appropriate expiration date and a record of such data shall be maintained. Accelerated studies, combined with basic stability information on the components, drug products, and container-closure system, may be used to support tentative expiration dates provided full shelf life studies are not available and are being conducted. Where data from accelerated studies are used to project a tentative expiration date that is beyond a date supported by actual shelf life studies, there must be stability studies conducted, including drug product testing at appropriate intervals, until the tentative expiration date is verified or the appropriate expiration date determined.

(c) For homeopathic drug products, the requirements of this section are as follows:
(1) There shall be a written assessment of stability based at least on testing or examination of the drug product for compatibility of the ingredients, and based on marketing experience with the drug product to indicate that there is no degradation of the product for the normal or expected period of use.
(2) Evaluation of stability shall be based on the same container-closure system in which the drug product is being marketed.

(d) Allergenic extracts that are labeled “No U.S. Standard of Potency” are exempt from the requirements of this section.

§ 211.167 Special testing requirements.
(a) For each batch of drug product purporting to be sterile and/or pyrogen-free, there shall be appropriate laboratory testing to determine conformance to such requirements. The test procedures shall be in writing and shall be followed.
(b) For each batch of ophthalmic ointment, there shall be appropriate testing to determine conformance to specifications regarding the presence of foreign particles and harsh or abrasive substances. The test procedures shall be in writing and shall be followed.
(c) For each batch of controlled-release dosage form, there shall be appropriate laboratory testing to determine conformance to the specifications for the rate of release of each active ingredient. The test procedures shall be in writing and shall be followed.

§ 211.170 Reserve samples.
(a) An appropriately identified reserve sample that is representative of each lot in each shipment of each active ingredient shall be retained. The reserve sample consists of at least twice the quantity necessary for all tests required to determine whether the active ingredient meets its established specifications, except for sterility and pyrogen testing. The retention time is as follows:
(1) For an active ingredient in a drug product other than those described in paragraphs (a) (2) and (3) of this section, the reserve sample shall be retained for 1 year after the expiration date of the last lot of the drug product containing the active ingredient.
(2) For an active ingredient in a radioactive drug product, except for nonradioactive reagent kits, the reserve sample shall be retained for:
   (i) Three months after the expiration date of the last lot of the drug product containing the active ingredient if the expiration dating period of the drug product is 30 days or less; or
   (ii) Six months after the expiration date of the last lot of the drug product containing the active ingredient if the expiration dating period of the drug product is more than 30 days.
(3) For an active ingredient in an OTC drug product that is exempt from bearing an expiration date under §211.137, the reserve sample shall be retained for 3 years after distribution of the last lot of the drug product containing the active ingredient.
(b) An appropriately identified reserve sample that is representative of each lot or batch of drug product shall be retained and stored under conditions consistent with product labeling. The reserve sample shall be stored in the same immediate container-closure system in which the drug product is marketed or in one that has essentially the same characteristics. The reserve sample consists of at least twice the quantity necessary to perform all the required tests, except those for sterility and pyrogens. Except for those for
drug products described in paragraph (b)(2) of this section, reserve samples from representative sample lots or batches selected by acceptable statistical procedures shall be examined visually at least once a year for evidence of deterioration unless visual examination would affect the integrity of the reserve sample. Any evidence of reserve sample deterioration shall be investigated in accordance with §211.192. The results of the examination shall be recorded and maintained with other stability data on the drug product. Reserve samples of compressed medical gases need not be retained. The retention time is as follows:

(1) For a drug product other than those described in paragraphs (b) (2) and (3) of this section, the reserve sample shall be retained for 1 year after the expiration date of the drug product.

(2) For a radioactive drug product, except for nonradioactive reagent kits, the reserve sample shall be retained for:

   (i) Three months after the expiration date of the drug product if the expiration dating period of the drug product is 30 days or less; or

   (ii) Six months after the expiration date of the drug product if the expiration dating period of the drug product is more than 30 days.

(3) For an OTC drug product that is exempt for bearing an expiration date under §211.137, the reserve sample must be retained for 3 years after the lot or batch of drug product is distributed.

§ 211.173 Laboratory animals.

Animals used in testing components, in-process materials, or drug products for compliance with established specifications shall be maintained and controlled in a manner that assures their suitability for their intended use. They shall be identified, and adequate records shall be maintained showing the history of their use.

§ 211.176 Penicillin contamination.

If a reasonable possibility exists that a non-penicillin drug product has been exposed to cross-contamination with penicillin, the non-penicillin drug product shall be tested for the presence of penicillin. Such drug product shall not be marketed if detectable levels are found when tested according to procedures specified in 'Procedures for Detecting and Measuring Penicillin Contamination in Drugs,' which is incorporated by reference. Copies are available from the Division of Research and Testing (HFD–470), Center for Drug Evaluation and Research, Food and Drug Administration, 5100 Paint Branch Pkwy., College Park, MD 20740, or available for inspection at the National Archives and Records Administration (NARA). For information on the availability of this material at NARA, call 202–741–6030, or go to:


8. 21 CFR Part 610—GENERAL BIOLOGICAL PRODUCTS STANDARDS

a. “§ 610.1 Tests prior to release required for each lot.

No lot of any licensed product shall be released by the manufacturer prior to the completion of tests for conformity with standards applicable to such product. Each applicable test shall be made on each lot after completion of all processes of manufacture which may affect compliance with the standard to which the test applies. The results of all tests performed shall be considered in determining whether or not the test results meet the test objective, except that a test result may be disregarded when it is established that the test is invalid due to causes unrelated to the product.”

b. “§ 610.2 Requests for samples and protocols; official release.

(a) Licensed biological products regulated by CBER. Samples of any lot of any licensed product together with the protocols showing results of applicable tests, may at any time be required to be sent to the Director, Center for Biologics Evaluation and Research (see mailing addresses in §600.2 of this chapter). Upon notification by the Director, Center for Biologics Evaluation and Research, a manufacturer shall not distribute a lot of a product until the lot is released by the Director, Center for Biologics Evaluation and Research: Provided, That the Director, Center for Biologics Evaluation and Research, shall not issue such notification except when deemed necessary for the safety, purity, or potency of the product.

(b) Licensed biological products regulated by CDER. Samples of any lot of any licensed product together with the protocols showing results of applicable tests, may at any time be required to be sent to the Director, Center for Drug Evaluation and Research (see mailing addresses in §600.2) for official release.
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Upon notification by the Director, Center for Drug Evaluation and Research, a manufacturer shall not distribute a lot of a biological product until the lot is released by the Director, Center for Drug Evaluation and Research: Provided, That the Director, Center for Drug Evaluation and Research shall not issue such notification except when deemed necessary for the safety, purity, or potency of the product.

c. “§ 610.11 General safety.

A general safety test for the detection of extraneous toxic contaminants shall be performed on biological products intended for administration to humans. The general safety test is required in addition to other specific tests prescribed in the additional standards for individual products in this subchapter, except that, the test need not be performed on those products listed in paragraph (g) of this section. The general safety test shall be performed as specified in this section, unless: Modification is prescribed in the additional standards for specific products, or variation is approved as a supplement to the product license under §610.9.

(a) Product to be tested. The general safety test shall be conducted upon a representative sample of the product in the final container from every final filling of each lot of the product. If any product is processed further after filling, such as by freeze-drying, sterilization, or heat treatment, the test shall be conducted upon a sample from each filling of each drying chamber run, sterilization chamber, or heat treatment bath.

(b) Test animals. Only overtly healthy guinea pigs weighing less than 400 grams each and mice weighing less than 22 grams each shall be used. The animals shall not have been used previously for any test purpose.

(c) Procedure. The duration of the general safety test shall be 7 days for both species, except that a longer period may be established for specific products in accordance with §610.9. Once the manufacturer has established a specific duration of the test period for a specific product, it cannot be varied subsequently, except, in accordance with §610.9. Each test animal shall be weighed and the individual weights recorded immediately prior to injection and on the last day of the test. Each animal shall be observed every working day. Any animal response including any which is not specific for or expected from the product and which may indicate a difference in its quality shall be recorded on the day such response is observed. The test product shall be administered as follows:

(1) Liquid product or freeze-dried product which has been reconstituted as directed on the label. Inject intraperitoneally 0.5 milliliter of the liquid product or the reconstituted product into each of at least two mice, and 5.0 milliliters of the liquid product or the reconstituted product into each of at least two guinea pigs.

(2) Freeze-dried product for which the volume of reconstitution is not indicated on the label. The route of administration, test dose, and diluent shall be as approved in accordance with §610.9. Administer the test product as approved on at least two mice and at least two guinea pigs.

(3) Nonliquid products other than freeze-dried product. The route of administration, test dose, and diluent shall be as in accordance with §610.9. Dissolve or grind and suspend the product in the approved diluent. Administer the test product as approved on at least two mice and at least two guinea pigs.

(d) Test requirements. A safety test is satisfactory if all animals meet all of the following requirements:

(1) They survive the test period.

(2) They do not exhibit any response which is not specific for or expected from the product and which may indicate a difference in its quality.

(3) They weigh no less at the end of the test period than at the time of injection.

(e) Repeat tests—(1) First repeat test. If a filling fails to meet the requirements of paragraph (d) of this section in the initial test, a repeat test may be conducted on the species which failed the initial test, as prescribed in paragraph (c) of this section. The filling is satisfactory only if each retest animal meets the requirements prescribed in paragraph (d) of this section.

(2) Second repeat test. If a filling fails to meet the requirements of the first repeat test, a second repeat test may be conducted on the species which failed the test: Provided, That 50 percent of the total number of animals in that species has survived the initial and first repeat tests. The second repeat test shall be conducted as prescribed in paragraph (c) of this section, except that the number of
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animals shall be twice that used in the first repeat test. The filling is satisfactory only if each second repeat test animal meets the requirements prescribed in paragraph (d) of this section.

(f) [Reserved]

(g) Exceptions—(1) The test prescribed in this section need not be performed for Whole Blood, Red Blood Cells, Cryoprecipitated AHF, Platelets, Plasma, or Cellular Therapy Products.

(2) For products other than those identified in paragraph (g)(1) of this section, a manufacturer may request from the Director, Center for Biologics Evaluation and Research or the Director, Center for Drug Evaluation and Research (see mailing addresses in §600.2 of this chapter), an exemption from the general safety test. The manufacturer must submit information as part of a biologics license application submission or supplement to an approved biologics license application establishing that because of the mode of administration, the method of preparation, or the special nature of the product a test of general safety is unnecessary to assure the safety, purity, and potency of the product or cannot be performed. The request must include alternate procedures, if any, to be performed. The Director, Center for Biologics Evaluation and Research or the Director, Center for Drug Evaluation and Research, upon finding that the manufacturer’s request justifies an exemption, may exempt the product from the general safety test subject to any condition necessary to assure the safety, purity, and potency of the product.”

d. “§ 610.11a Inactivated influenza vaccine, general safety test.

For inactivated influenza vaccine, the general safety test shall be conducted in the manner indicated in §610.11 of this chapter except that, with reference to guinea pigs, the test shall be satisfied if the product provides satisfactory results using either the subcutaneous or intraperitoneal injection of 5.0 milliliters of inactivated influenza vaccine into each guinea pig. The requirements for general safety for inactivated influenza vaccine shall not be considered to be satisfied unless each lot of influenza vaccine is assayed for endotoxin in comparison to a reference preparation provided by the Food and Drug Administration, and such lot is found to contain no more endotoxin than the reference preparation.”

e. “§ 610.13 Purity.

Products shall be free of extraneous material except that which is unavoidable in the manufacturing process described in the approved biologics license application. In addition, products shall be tested as provided in paragraphs (a) and (b) of this section.

(a) (1) Test for residual moisture. Each lot of dried product shall be tested for residual moisture and shall meet and not exceed established limits as specified by an approved method on file in the biologics license application. The test for residual moisture may be exempted by the Director, Center for Biologics Evaluation and Research or the Director, Center for Drug Evaluation and Research, when deemed not necessary for the continued safety, purity, and potency of the product.

(2) Records. Appropriate records for residual moisture under paragraph (a)(1) of this section shall be prepared and maintained as required by the applicable provisions of §§211.188 and 211.194 of this chapter.

(b) Test for pyrogenic substances. Each lot of final containers of any product intended for use by injection shall be tested for pyrogenic substances by intravenous injection into rabbits as provided in paragraphs (b) (1) and (2) of this section: Provided, That notwithstanding any other provision of Subchapter F of this chapter, the test for pyrogenic substances is not required for the following products: Products containing formed blood elements; Cryoprecipitate; Plasma; Source Plasma; Normal Horse Serum; bacterial, viral, and rickettsial vaccines and antigens; toxoids; toxins; allergic extracts; venoms; diagnostic substances and trivalent organic arsenicals.

(1) Test dose. The test dose for each rabbit shall be at least 3 milliliters per kilogram of body weight of the rabbit and also shall be at least equivalent proportionately, on a body weight basis, to the maximum single human dose recommended, but need not exceed 10 milliliters per kilogram of body weight of the rabbit, except that: (i) Regardless of the human dose recommended, the test dose per kilogram of body weight of each rabbit shall be at least 1 milliliter for immune globulins derived from human blood; (ii) for Streptokinase, the test dose shall be at least equivalent proportionately, on a body weight basis, to the maximum single human dose recommended.

(2) Test procedure, results, and interpretation; standards to be met. The test for pyrogenic substances shall be performed according to the requirements specified in United States Pharmacopeia XX.
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(3) Retest. If the lot fails to meet the test requirements prescribed in paragraph (b)(2) of this section, the test may be repeated once using five other rabbits. The temperature rises recorded for all eight rabbits used in testing shall be included in determining whether the requirements are met. The lot meets the requirements for absence of pyrogens if not more than three of the eight rabbits show individual rises in temperature of 0.6 °C or more, and if the sum of the eight individual maximum temperature rises does not exceed 3.7 °C.

f. “§ 610.14 Identity.
The contents of a final container of each filling of each lot shall be tested for identity after all labeling operations shall have been completed. The identity test shall be specific for each product in a manner that will adequately identify it as the product designated on final container and package labels and circulars, and distinguish it from any other product being processed in the same laboratory. Identity may be established either through the physical or chemical characteristics of the product, inspection by macroscopic or microscopic methods, specific cultural tests, or in vitro or in vivo immunological tests.”

g. “§ 610.15 Constituent materials.
(a) Ingredients, preservatives, diluents, adjuvants. All ingredients used in a licensed product, and any diluent provided as an aid in the administration of the product, shall meet generally accepted standards of purity and quality. Any preservative used shall be sufficiently nontoxic so that the amount present in the recommended dose of the product will not be toxic to the recipient, and in the combination used it shall not denature the specific substances in the product to result in a decrease below the minimum acceptable potency within the dating period when stored at the recommended temperature. Products in multiple-dose containers shall contain a preservative, except that a preservative need not be added to Yellow Fever Vaccine; Poliovirus Vaccine Live Oral; viral vaccines labeled for use with the jet injector; dried vaccines when the accompanying diluent contains a preservative; or to an Allergenic Product in 50 percent or more volume in volume (v/v) glycerin. An adjuvant shall not be introduced into a product unless there is satisfactory evidence that it does not affect adversely the safety or potency of the product. The amount of aluminum in the recommended individual dose of a biological product shall not exceed:
(1) 0.85 milligrams if determined by assay;
(2) 1.14 milligrams if determined by calculation on the basis of the amount of aluminum compound added; or
(3) 1.25 milligrams determined by assay provided that data demonstrating that the amount of aluminum used is safe and necessary to produce the intended effect are submitted to and approved by the Director, Center for Biologics Evaluation and Research or the Director, Center for Drug Evaluation and Research (see mailing addresses in §600.2 of this chapter).
(b) Extraneous protein; cell culture produced vaccines. Extraneous protein known to be capable of producing allergenic effects in human subjects shall not be added to a final virus medium of cell culture produced vaccines intended for injection. If serum is used at any stage, its calculated concentration in the final medium shall not exceed 1:1,000,000.
(c) Antibiotics. A minimum concentration of antibiotics, other than penicillin, may be added to the production substrate of viral vaccines.”

h. “§ 610.30 Test for Mycoplasma.
Except as provided otherwise in this subchapter, prior to clarification or filtration in the case of live virus vaccines produced from in vitro living cell cultures, and prior to inactivation in the case of inactivated virus vaccines produced from such living cell cultures, each virus harvest pool and control fluid pool shall be tested for the presence of Mycoplasma, as follows:
Samples of the virus for this test shall be stored either (1) between 2 and 8 °C for no longer than 24 hours, or (2) at 20 °C or lower if stored for longer than 24 hours. The test shall be performed on samples of the viral harvest pool and on control fluid pool obtained at the time of viral harvest, as follows: No less than 2.0 ml. of each sample shall be inoculated in evenly distributed amounts over the surface of no less than 0 plates of at least two agar media.
No less than 1.0 ml. of sample shall be inoculated into each of four tubes containing 10 ml. of a semisolid broth medium.
The media shall be such as have been shown to be capable of detecting known Mycoplasma and each test shall include control cultures of at least two known strains of Mycoplasma, one of which must be M.
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pneumoniae. One half of the plates and two tubes of broth shall be incubated aerobically at 36 °C ± 1 °C and the remaining plates and tubes shall be incubated anaerobically at 36 °C ± 1 °C in an environment of 5-10 percent CO2 in N2. Aerobic incubation shall be for a period of no less than 14 days and the broth in the two tubes shall be tested after 3 days and 14 days, at which times 0.5 ml of broth from each of the two tubes shall be combined and subinoculated on to no less than 4 additional plates and incubated aerobically. Anaerobic incubation shall be for no less than 14 days and the broth in the two tubes shall be tested after 3 days and 14 days, at which times 0.5 ml of broth from each of the two tubes shall be combined and subinoculated onto no less than four additional plates and incubated anaerobically. All inoculated plates shall be incubated for no less than 14 days, at which time observation for growth of Mycoplasma shall be made at a magnification of no less than 300×. If the Dienes Methylene Blue-Azure dye or an equivalent staining procedure is used, no less than a one square cm. plug of the agar shall be excised from the inoculated area and examined for the presence of Mycoplasma. The presence of the Mycoplasma shall be determined by comparison of the growth obtained from the test samples with that of the control cultures, with respect to typical colonial and microscopic morphology.

The virus pool is satisfactory for vaccine manufacture if none of the tests on the samples show evidence of the presence of Mycoplasma.”

9. **42 U.S.C. Sections 300aa-1 through 300aa-34.** — Especially:
   a. “Sec. 300aa-22. Standards of responsibility
      (a) General rule
         Except as provided in subsections (b), (c), and (e) of this section State law shall apply to a civil action brought for damages for a vaccine-related injury or death.
      (b) Unavoidable adverse side effects; warnings
         (1) No vaccine manufacturer shall be liable in a civil action for damages arising from a vaccine-related injury or death associated with the administration of a vaccine after October 1, 1988, if the injury or death resulted from side effects that were unavoidable even though the vaccine was properly prepared and was accompanied by proper directions and warnings.
         (2) For purposes of paragraph (1), a vaccine shall be presumed to be accompanied by proper directions and warnings if the vaccine manufacturer shows that it complied in all material respects with all requirements under the Federal Food, Drug, and Cosmetic Act [21 U.S.C. 301 et seq.] and section 262 of this title (including regulations issued under such provisions) applicable to the vaccine and related to vaccine-related injury or death for which the civil action was brought unless the plaintiff shows:
            (A) that the manufacturer engaged in the conduct set forth in subparagraph (A) or (B) of section 300aa-23(d)(2) of this title, or
            (B) by clear and convincing evidence that the manufacturer failed to exercise due care notwithstanding its compliance with such Act and section (and regulations issued under such provisions).
      (c) Direct warnings
         No vaccine manufacturer shall be liable in a civil action for damages arising from a vaccine-related injury or death associated with the administration of a vaccine after October 1, 1988, solely due to the manufacturer’s failure to provide direct warnings to the injured party (or the injured party’s legal representative) of the potential dangers resulting from the administration of the vaccine manufactured by the manufacturer.
      (d) Construction
         The standards of responsibility prescribed by this section are not to be construed as authorizing a person who brought a civil action for damages against a vaccine manufacturer for a vaccine-related injury or death in which damages were denied or which was dismissed with prejudice to bring a new civil action against such manufacturer for such injury or death.
      (e) Preemption
         No State may establish or enforce a law which prohibits an individual from bringing a civil action against a vaccine manufacturer for damages for a vaccine-related injury or death if such civil action is not barred by this part.”
   b. “Sec. 300aa-23. Trial
      (a) General rule
         A civil action against a vaccine manufacturer for damages for a vaccine-related injury or death associated with the administration of a vaccine after October 1, 1988, which is not barred by section 300aa-11(a)(2) of this title shall be tried in three stages.
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(b) Liability
The first stage of such a civil action shall be held to determine if a vaccine manufacturer is liable under section 300aa-22 of this title.

c) General damages
The second stage of such a civil action shall be held to determine the amount of damages (other than punitive damages) a vaccine manufacturer found to be liable under section 300aa-22 of this title shall be required to pay.

d) Punitive damages
(1) If sought by the plaintiff, the third stage of such an action shall be held to determine the amount of punitive damages a vaccine manufacturer found to be liable under section 300aa-22 of this title shall be required to pay.

(2) If in such an action the manufacturer shows that it complied, in all material respects, with all requirements under the Federal Food, Drug, and Cosmetic Act [21 U.S.C. 301 et seq.] and this chapter applicable to the vaccine and related to the vaccine injury or death with respect to which the action was brought, the manufacturer shall not be held liable for punitive damages unless the manufacturer engaged in -
(A) fraud or intentional and wrongful withholding of information from the Secretary during any phase of a proceeding for approval of the vaccine under section 262 of this title,
(B) intentional and wrongful withholding of information relating to the safety or efficacy of the vaccine after its approval, or
(C) other criminal or illegal activity relating to the safety and effectiveness of vaccines, which activity related to the vaccine-related injury or death for which the civil action was brought.

e) Evidence
In any stage of a civil action, the Vaccine Injury Table, any finding of fact or conclusion of law of the United States Court of Federal Claims or a special master in a proceeding on a petition filed under section 300aa-11 of this title and the final judgment of the United States Court of Federal Claims and subsequent appellate review on such a petition shall not be admissible.

Sec. 300aa-25. Recording and reporting of information
(a) General rule
Each health care provider who administers a vaccine set forth in the Vaccine Injury Table to any person shall record, or ensure that there is recorded, in such person's permanent medical record (or in a permanent office log or file to which a legal representative shall have access upon request) with respect to each such vaccine -
(1) the date of administration of the vaccine,
(2) the vaccine manufacturer and lot number of the vaccine,
(3) the name and address and, if appropriate, the title of the health care provider administering the vaccine,

and
(4) any other identifying information on the vaccine required pursuant to regulations promulgated by the Secretary.

(b) Reporting
(1) Each health care provider and vaccine manufacturer shall report to the Secretary -
(A) the occurrence of any event set forth in the Vaccine Injury Table, including the events set forth in section 300aa-14(b) of this title which occur within 7 days of the administration of any vaccine set forth in the Table or within such longer period as is specified in the Table or section,
(B) the occurrence of any contraindicating reaction to a vaccine which is specified in the manufacturer's package insert, and
(C) such other matters as the Secretary may by regulation require.

Reports of the matters referred to in subparagraphs (A) and (B) shall be made beginning 90 days after December 22, 1987. The Secretary shall publish in the Federal Register as soon as practicable after such date a notice of the reporting requirement.

(2) A report under paragraph (1) respecting a vaccine shall include the time periods after the administration of such vaccine within which vaccine-related illnesses, disabilities, injuries, or conditions, the symptoms and manifestations of such illnesses, disabilities, injuries, or conditions, or deaths occur, and the manufacturer and lot number of the vaccine.

(3) The Secretary shall issue the regulations referred to in paragraph (1)(C) within 180 days of December 22, 1987.

(c) Release of information
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(1) Information which is in the possession of the Federal Government and State and local governments under this section and which may identify an individual shall not be made available under section 552 of title 5, or otherwise, to any person except -
   (A) the person who received the vaccine, or
   (B) the legal representative of such person.

(2) For purposes of paragraph (1), the term "information which may identify an individual" shall be limited to the name, street address, and telephone number of the person who received the vaccine and of that person's legal representative and the medical records of such person relating to the administration of the vaccine, and shall not include the locality and State of vaccine administration, the name of the health care provider who administered the vaccine, the date of the vaccination, or information concerning any reported illness, disability, injury, or condition resulting from the administration of the vaccine, any symptom or manifestation of such illness, disability, injury, or condition, or death resulting from the administration of the vaccine.

(3) Except as provided in paragraph (1), all information reported under this section shall be available to the public.”

d. “Sec. 300aa-27. Mandate for safer childhood vaccines
   (a) General rule
   In the administration of this part and other pertinent laws under the jurisdiction of the Secretary, the Secretary shall -
   (1) promote the development of childhood vaccines that result in fewer and less serious adverse reactions than those vaccines on the market on December 22, 1987, and promote the refinement of such vaccines, and
   (2) make or assure improvements in, and otherwise use the authorities of the Secretary with respect to, the licensing, manufacturing, processing, testing, labeling, warning, use instructions, distribution, storage, administration, field surveillance, adverse reaction reporting, and recall of reactogenic lots or batches, of vaccines, and research on vaccines, in order to reduce the risks of adverse reactions to vaccines.

   (b) Task force
   (1) The Secretary shall establish a task force on safer childhood vaccines which shall consist of the Director of the National Institutes of Health, the Commissioner of the Food and Drug Administration, and the Director of the Centers for Disease Control.
   (2) The Director of the National Institutes of Health shall serve as chairman of the task force.
   (3) In consultation with the Advisory Commission on Childhood Vaccines, the task force shall prepare recommendations to the Secretary concerning implementation of the requirements of subsection (a) of this section.

   (c) Report
   Within 2 years after December 22, 1987, and periodically thereafter, the Secretary shall prepare and transmit to the Committee on Energy and Commerce of the House of Representatives and the Committee on Labor and Human Resources of the Senate a report describing the actions taken pursuant to subsection (a) of this section during the preceding 2-year period.”

e. “Sec. 300aa-31. Citizen's actions
   (a) General rule
   Except as provided in subsection (b) of this section, any person may commence in a district court of the United States a civil action on such person's own behalf against the Secretary where there is alleged a failure of the Secretary to perform any act or duty under this part.

   (b) Notice
   No action may be commenced under subsection (a) of this section before the date which is 60 days after the person bringing the action has given written notice of intent to commence such action to the Secretary.

   (c) Costs of litigation
   The court, in issuing any final order in any action under this section, may award costs of litigation (including reasonable attorney and expert witness fees) to any plaintiff who substantially prevails on one or more significant issues in the action.

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“108 S.Ct. 1954
100 L.Ed.2d 531, 56 USLW 4549
(Cite as: 486 U.S. 531, 108 S.Ct. 1954)

[1] United States v. 78(12)
393k78(12) Most Cited Cases
In determining whether discretionary function exception bars suit against United States, court must consider whether action is matter of choice for acting employee since conduct cannot be discretionary unless it involves element of judgment or choice. 28 U.S.C.A. § 2680(a).

[2] United States v. 78(12)
393k78(12) Most Cited Cases
Discretionary function exception to suits against United States will not apply when federal statute, regulation, or policies specifically prescribes course of action for employee to follow. 28 U.S.C.A. § 2680(a).

[3] United States v. 78(12)
393k78(12) Most Cited Cases
Discretionary function exception to suits against United States protects only governmental actions and decisions based on considerations of public policy. 28 U.S.C.A. § 2680(a).

[4] United States v. 78(12)
393k78(12) Most Cited Cases
Discretionary function exception to Tort Claims Act does not preclude liability for any and all acts arising out of federal agencies’ regulatory programs, but insulates from liability only those governmental actions and decisions that involve element of judgment or choice and that are based on public policy considerations. 28 U.S.C.A. § 2680(a).

[5] United States v. 78(12)
393k78(12) Most Cited Cases
Cause of action based upon allegation that National Institutes of Health’s Division of Biologic Standards licensed oral polio vaccine without first receiving required safety data was not barred by discretionary function exception to Federal Tort Claims Act; Division has no discretion to issue license under such circumstances, and in doing so violates specific statutory regulatory directive. 28 U.S.C.A. § 2680(a); Public Health Service Act, § 351(a, d), as amended, 42 U.S.C.A. § 262(a, d).
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108 S.Ct. 1954
100 L.Ed.2d 531, 56 USL.W 4549
(Cite as: 486 U.S. 531, 108 S.Ct. 1954)

[6] United States & 78(12)
393k78(12) Most Cited Cases

Cause of action based upon National Institutes of Health's Division of Biologic Standards, licensing of oral polio vaccine, either without determining whether vaccine complied with regulatory standards or after determining that vaccine failed to comply, would not be barred by discretionary function exception to Tort Claims Act; agency has no discretion to deviate from mandated procedure precluding issuance of license except upon examination of product and determination that product complies with all regulatory standards. 28 U.S.C.A. § 2680(a); Public Health Service Act, § 351(a, d), as amended, 42 U.S.C.A. § 262(a, d).

[7] United States & 78(12)
393k78(12) Most Cited Cases

In suit charging agency with failing to act in accord with specific mandatory directive, discretionary function exception to Tort Claims Act does not apply. 28 U.S.C.A. § 2680(a).

[8] United States ~78(12)
393k78(12) Most Cited Cases

Whether cause of action that National Institutes of Health's Division of Biologic Standards made determination that oral polio vaccine complied with regulatory standards, but that determination was incorrect, was barred by discretionary function exception to Tort Claims Act depended on whether agency officials making determination of compliance permissibly exercised policy choice; however, since parties failed to address question in detail, question would not be decided by Supreme Court, but rather, left to district court. 28 U.S.C.A. § 2680(a); Public Health Service Act, § 351(a, d), as amended, 42 U.S.C.A. § 262(a, d).

[9] United States ~8(12)
393k78(12) Most Cited Cases

Discretionary function exception to Tort Claims Act barred any claims that challenged Food and Drug Administration's Bureau of Biologies' formulation of policy as to appropriate way in which to regulate release of oral polio vaccine; in addition, if policies and programs formulated by Bureau allowed room for implementing officials to make independent policy judgments, discretionary function exception protected acts taken by those officials in exercise of that discretion. 28 U.S.C.A. § 2680(a).

[10] United States & 78(12)
393k78(12) Most Cited Cases

Discretionary function exception to Tort Claims Act did not bar claim alleging that, under authority granted by regulations, the Food and Drug Administration adopted policy of testing all lots of oral polio vaccine for compliance with safety standards and preventing the public distribution of any lot that failed to comply, and that, notwithstanding that mandatory policy, FDA knowingly approved release of unsafe lot. 28 U.S.C.A. § 2680(a).

**1955 *531 Syllabus [FN*]

FN* The syllabus constitutes no part of the opinion of the Court but has been prepared by the Reporter of Decisions for the convenience of the reader. See United States v. Detroit Lumber Co., 200 U.S. 321, 337, 26 S.Ct. 282, 287, SOL.Ed. 499.

A provision of the Federal Tort Claims Act (FTCA) excepts from statutory liability any claim "based upon [a federal agency's or employee's] exercise or performance or the failure to exercise or perform a discretionary function or duty." Upon contracting a severe case of polio after ingesting a dose of Orimune, an oral polio vaccine manufactured by Lederle Laboratories, petitioner Kevan Berkovitz, a minor, joined by his parents (also petitioners) acting as guardians, **1956 filed an FTCA suit alleging violations of federal law and policy by the National Institutes of Health's Division of Biologic Standards (DBS) in licensing Lederle to produce Orimune, and by the Bureau of Biologics of the Food and Drug Administration (FDA) in approving the release to the public of the particular lot of vaccine containing Berkovitz's dose. The District Court denied the Government's motion to dismiss the suit for lack of subject-matter jurisdiction, but the Court of Appeals reversed. Although rejecting the Government's argument that the discretionary function exception bars all claims arising out of federal agencies' regulatory activities, the court held that the licensing and release of polio vaccines are wholly discretionary actions protected by the exception.
Held:

1. The language, purpose, and legislative history of the discretionary function exception, as well as its interpretation in this Court’s decisions, establish that the exception does not preclude liability for any and all acts arising out of federal agencies’ regulatory programs, but insulates from liability only those governmental actions and decisions that involve an element of judgment or choice and that are based on public policy considerations. Pp. 1958-1960.

2. The Court of Appeals erred in holding that the discretionary function exception bars petitioners’ claims. P. 1960-1965.

(a) Statutory and regulatory provisions require the DBS, prior to issuing a license for a product such as Orimune, to receive all data which the manufacturer is required to submit, to examine the product, and to make a determination that it complies with safety standards. Thus, a cause of action based on petitioner’s allegation that the DBS licensed Orimune without first receiving the required safety data is not barred by the discretionary function exception, since the DBS has no discretion to issue a license under such circumstances, and doing so would violate a specific statutory and regulatory directive. Petitioners’ other claim—that the DBS licensed Orimune even though the vaccine did not comply with certain regulatory safety standards—if interpreted to mean that the DBS issued the license without determining compliance with the standards or after determining a failure to comply, also is not barred by the discretionary function exception, since the claim charges the agency with failing to act in accordance with specific mandatory directives, as to which the DBS has no discretion. However, if this claim is interpreted to mean that the DBS made an incorrect compliance determination, the question of the discretionary function exception’s applicability, turns on whether the DBS officials making that determination permissibly exercise policy choice, a point that is not clear from the record and therefore must be decided by the District Court if petitioners choose to press this interpretation. pp. 1960-1963.

(b) Although the regulatory scheme governing the public release of vaccine lots allows the FDA to determine the appropriate manner in which to regulate, petitioners have alleged that, under the authority granted by the regulations, the FDA has adopted a policy of testing all lots for compliance with safety standards and of preventing the public distribution of any lot that fails to comply, and that, notwithstanding this mandatory policy, the FDA knowingly approved the release of the unsafe lot in question. Accepting these allegations as true, as is necessary in reviewing a dismissal, the holding that the discretionary function exception barred petitioners’ claim was improper, since the acts complained of do not involve the permissible exercise of discretion to release a noncomplying lot on the basis of policy considerations. Pp 1963-1965.

822 F.2d 1322 (CA3 1987), reversed and remanded.

MARSHALL, J. delivered the opinion for a unanimous Court.

**1957** Ellen M. Viakley argued the cause for petitioners. With her on the briefs were Gary S. Gildin and Paul R. Friedman.

Michael K. Kellogg argued the cause for the United States. With him on the brief were Solicitor General Fried, Assistant Attorney General Bolton, Deputy Solicitor General Ayer, John F. Cordes, William Cole, Thomas Scarlett, and Ann H. Wion.*

* Lloyd N. Cutler, James Robertson, and Ronald J. Greene filed a brief for Lederle Laboratories as amicus curiae.

*533 Justice MARSHALL delivered the opinion of the Court.

The question in this case is whether the discretionary function exception of the Federal Tort Claims Act (FTCA or Act), 28 U.S.C. § 2680(a), bars a suit based on the Government’s licensing of an oral polio vaccine and on its subsequent approval of the release of a specific lot of that vaccine to the public.

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Appendix A
Reviewer's General References From Before 2006

108 S.Ct. 1954
100 L.Ed.2d 531, 56 USL W 4549
(Cite as: 486 U.S. 531, 108 S.Ct. 1954)

On May 10, 1979, Kevan Berkovitz, then a 2-month-old infant, ingested a dose of Orimune, an oral polio vaccine manufactured by Lederle Laboratories. Within one month, he contracted a severe case of polio. The disease left Berkovitz almost completely paralyzed and unable to breathe without the assistance of a respirator. The Communicable Disease Center, an agency of the Federal Government, determined that Berkovitz had contracted polio from the vaccine.

Berkovitz, joined by his parents as guardians, subsequently filed suit against the United States in Federal District Court. The complaint alleged that the United States was liable for his injuries under the FTCA, 28 U.S.C. §§ 1346(b), 2674, because the Division of Biologic Standards (DBS), then a part of the National Institutes of Health, had acted wrongfully in licensing Lederle Laboratories to produce Orimune and because the Bureau of Biologics of the Food and Drug Administration (FDA) had acted wrongfully in approving release to the public of the particular lot of vaccine containing Berkovitz's dose. According to petitioners, these actions violated federal law and policy regarding the inspection and approval of polio vaccines.

FNI. Petitioners also sued Lederle Laboratories in a separate civil action. That suit was settled before the instant case was filed.

The Government moved to dismiss the suit for lack of subject-matter jurisdiction on the ground that the agency actions fell within the discretionary function exception of the FTCA. The District Court denied this motion, concluding that neither the licensing of Orimune nor the release of a specific lot of that vaccine to the public was a "discretionary function" within the meaning of the FTCA. Civ. Action No. 84-2893 (WD Pa., Apr. 30, 1986). At the Government's request, the District Court certified its decision for immediate appeal to the Third Circuit pursuant to 28 U.S.C. § 1292(b), and the Court of Appeals accepted jurisdiction.

A divided panel of the Court of Appeals reversed. 822 F.2d 1322 (1987). The court initially rejected the Government's argument that the discretionary function exception bars all claims arising out of the regulatory activities of federal agencies. The court stated that "the discretionary function exception is inapplicable to non-discretionary regulatory actions," id., at 1328, and noted that employees of regulatory agencies have no discretion to violate the command of federal statutes or regulations. Contrary to petitioners' claim, however, the court held that federal law imposed no duties on federal agencies with respect to the licensing of polio virus vaccines or the approval of the distribution of particular vaccine lots to the public. Likening the applicable regulatory scheme to the scheme found to confer discretionary regulatory authority in United States v. Varig Airlines, 467 U.S. 797, 104 S.Ct. 2755, 81 L.Ed.2d 660 (1984), the court concluded that the licensing and release of polio vaccines were wholly discretionary actions and, as such, could not form the basis for suit against the United States. A dissenting judge argued that the relevant statutes and regulations obligated the DBS to require the submission of test data relating to a vaccine from the manufacturer and to deny a license when the test data showed that the vaccine failed to conform with applicable safety standards. Reading the complaint in this case as alleging a failure on the part of the DBS to act in accordance with these directives, the dissenting judge concluded that the discretionary function exception did not bar petitioners' suit.

We granted certiorari, 484 U.S. 1003, 108 S.Ct. 692, 98 L.Ed.2d 645 (1988), to resolve a conflict in the Circuits regarding the effect of the discretionary function exception on claims arising from the Government's regulation of polio vaccines. Compare 822 F.2d 1322, supra, with Baker v. United States, 817 F.2d 560, 564-566 (CA9 1987) (holding that discretionary function exception did not bar suit alleging a negligent decision to license a polio vaccine); Loge v. United States, 662 F.2d 1268, 1272-1273 (CA8 1981) (holding that discretionary function exception did not bar suit alleging negligence in both the licensing of a polio vaccine and the release of a particular vaccine lot). We now reverse the Third Circuit's judgment.

II

The FTCA, 28 U.S.C. § 1346(b), generally authorizes suits against the United States for damages
"for injury or loss of property, or personal injury or death caused by the negligent or wrongful act or omission of any employee of the Government while acting within the scope of his office or employment, under circumstances where the United States, if a private person, would be liable to the claimant in accordance with the law of the place where the act or omission occurred." [FN2]

FN2. There is currently no dispute in this case as to whether petitioners have stated a claim that falls within this general waiver of immunity. Although the Government raised this issue in its motion to dismiss petitioners' suit, the District Court found that the complaint stated a claim under the relevant state law, and the Government declined to request certification of this decision for immediate appeal.

The Act includes a number of exceptions to this broad waiver of sovereign immunity. The exception relevant to this case provides that no liability shall lie for

"[a]ny claim ...based upon the exercise or performance or the failure to exercise or perform a discretionary function or duty on the part of a federal agency or an employee of the Government, whether or not the discretion involved be abused." 28 U.S.C. § 2680(a).

*536 This exception, as we stated in our most recent opinion on the subject, "marks the boundary between Congress' willingness to impose tort liability upon the United States and its desire to protect certain governmental activities from exposure to suit by private individuals." United States v. Varig Airlines, 467 U.S. at 808, 104 S.Ct., at 2761-2762.

[1][2] The determination of whether the discretionary function exception bars a suit against the Government is guided by several established principles. This Court stated in Varig that "it is the nature of the conduct, rather than the status of the actor, that governs whether the discretionary function exception applies in a given case." Id., at 813, 104 S.Ct., at 2764. In examining the nature of the challenged conduct, a court must first consider whether the action is a matter of choice for the acting employee. This inquiry is mandated by the language of the exception; conduct cannot be discretionary unless it involves an element of judgment or choice. See Dalehite v. United States, 346 U.S. 15, 34, 73 S.Ct. 956, 967, 97 L.Ed. 1472 (1953) (stating that the exception protects "the discretion of the executive or the administrator to act according to one's judgment of the best course").

Thus, the discretionary function exception will not apply when a federal statute, regulation, or policy specifically prescribes a course of action for an employee to follow. In this event, the employee has no rightful option but to adhere to the **1959 directive. And if the employee's conduct cannot appropriately be the product of judgment or choice, then there is no discretion in the conduct for the discretionary function exception to protect. Cf. Westfall v. Erwin, 484 U.S. 292, 296-297, 108 S.Ct. 580, ----, 98 L.Ed.2d 619 (1988) (recognizing that conduct that is not the product of independent judgment will be unaffected by threat of liability).

[3] Moreover, assuming the challenged conduct involves an element of judgment, a court must determine whether that judgment is of the kind that the discretionary function exception was designed to shield. The basis for the discretionary function exception was Congress' desire to "prevent judicial second-guessing of legislative and administrative decisions grounded in social, economic, and political policy through the medium of an action in tort." United States v. Varig Airlines, supra, at 814, 104 S.Ct., at 2764-2765. The exception, properly construed, therefore protects only governmental actions and decisions based on considerations of public policy. See Dalehite v. United States, supra, at 36, 73 S.Ct., at 968 ("Where there is room for policy judgment and decision there is discretion"). In sum, the discretionary function exception insulates the Government from liability if the action challenged in the case involves the permissible exercise of policy judgment.

This Court's decision in Varig Airlines illustrates these propositions. The two cases resolved in that decision were tort suits by the victims of airplane accidents who alleged that the Federal Aviation Administration (FAA) had acted negligently in certifying certain airplanes for operation. The Court characterized the suits as challenging the FAA's decision to certify the airplanes without first inspecting them and held that this decision was a discretionary act for which the Government was

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immune from liability. In reaching this result, the Court carefully reviewed the statutory and regulatory scheme governing the inspection and certification of airplanes. Congress had given the Secretary of Transportation broad authority to establish and implement a program for enforcing compliance with airplane safety standards. In the exercise of that authority, the FAA, as the Secretary's designee, had devised a system of "spot-checking" airplanes for compliance. This Court first held that the establishment of that system was a discretionary function within the meaning of the FTCA because it represented a policy determination as to how best to "accommodate[e] the goal of air transportation safety and the reality of finite agency resources." 467 U.S., at 820, 104 S.Ct., at 2767-2768. The Court then stated that the discretionary function exception also protected "the acts of FAA employees in executing the 'spot-check' program" because under this program the employees "were specifically empowered to *538 make policy judgments regarding the degree of confidence that might reasonably be placed in a given manufacturer, the need to maximize compliance with FAA regulations, and the efficient allocation of agency resources." Ibid. Thus, the Court held the challenged acts protected from liability because they were within the range of choice accorded by federal policy and law and were the results of policy determinations. [FN3]

[4] In restating and clarifying the scope of the discretionary function exception, we intend specifically to reject the Government's argument, pressed both in this Court and the Court of Appeals, that the **1960 exception precludes liability for any and all acts arising out of the regulatory programs of federal agencies. That argument is rebutted first by the language of the exception, which protects "discretionary" functions, rather than "regulatory" functions. The significance of Congress' choice of language is supported by the legislative history. As this Court previously has indicated, the relevant legislative materials demonstrate that the exception was designed to cover not all acts of regulatory agencies and their employees, but only such acts as are "discretionary" in nature. [FN4] See Dalehite v. United States, supra, 346 U.S., at 33-34, 73 S.Ct., at 966-967. *539 This coverage accords with Congress' purpose in enacting the exception: to prevent "[j]udicial intervention in ...the political, social, and economic judgments" of governmental--including regulatory—agencies. United States v. Varig Airlines, 467 U.S., at 820, 104 S.Ct., at 2767-2768. Moreover, this Court twice before has rejected a variant of the Government's position. See Indian Towing Co. v. United States, 350 U.S. 61, 64-65, 76 S.Ct. 122, 124, 100 L.Ed. 48 (1955) (disapproving argument that FTCA precludes liability for the performance of "uniquely governmental functions"); Rayonier, Inc. v. United States, 352 U.S. 315, 318-319, 77 S.Ct. 374, 376-377, 1 L.Ed.2d 354 (1957) (same). [FN5] And in Varig, we ignored the precise argument the Government makes in this case, focusing instead on the particular nature of the regulatory conduct at issue. To the extent we have not already put the Government's argument to rest, we do so now. The discretionary function exception applies only to conduct that involves the permissible exercise of policy judgment. The question in this case is whether the governmental activities challenged by petitioners are of this discretionary nature.

FN3. The decision in Indian Towing Co. v. United States, 350 u.s. 61, 76 S.Ct. 122, 100 L.Ed. 48 (1955), also illuminates the appropriate scope of the discretionary function exception. The plaintiff in that case sued the Government for failing to maintain a lighthouse in good working order. The Court stated that the initial decision to undertake and maintain lighthouse service was a discretionary judgment. See id., at 69, 76 S.Ct., at 126-127. The Court held, however, that the failure to maintain the lighthouse in good condition subjected the Government to suit under the FTCA. See ibid. The latter course of conduct did not involve any permissible exercise of policy judgment.

FN4. The House of Representatives Report on the final version of the FTCA discussed the application of the discretionary function exception to the activities of regulatory agencies by stating that it would preclude application of the Act to "a claim against a regulatory agency, such
as the Federal Trade Commission or the Securities and Exchange Commission, based upon an alleged abuse of discretionary authority by an officer or employee, whether or not negligence is alleged to have been involved … The bill is not intended to authorize a suit for damages to test the validity of or provide a remedy on account of such discretionary acts even though negligently performed and involving an abuse of discretion. Nor is it desirable or intended that the constitutionality of legislation, or the legality of a rule or regulation should be tested through the medium of a damage suit for tort. However, the common-law torts of employees of regulatory agencies would be included within the scope of the bill to the same extent as torts of nonregulatory agencies. “H.R.Rep. No. 1287, 79th Cong., 1st Sess., 6 (1945). This passage illustrates that Congress intended the discretionary function exception to apply to the discretionary acts of regulators, rather than to all regulatory acts.

FN5. The Government’s position in this case at times appears to replicate precisely the position expressly rejected in Indian Towing and Rayonier. See Brief for United States 20 (arguing that Congress intended to preserve immunity for “core governmental function[s]”); id., at 16.

III

Petitioners’ suit raises two broad claims. First, petitioners assert that the DBS violated a federal statute and accompanying regulations in issuing a license to Lederle Laboratories to produce Orimune. Second, petitioners argue that the Bureau of Biologics of the FDA violated federal regulations and policy in approving the release of the particular lot of Orimune that contained Kevan Berkovitz’s dose. We examine each of these broad claims by reviewing the applicable regulatory scheme and petitioners’ specific allegations of agency wrongdoing. [FN6] Because the decision **1961** we review adjudicated a motion to dismiss, we accept all of the factual allegations in petitioners’ complaint as true and ask whether, in these circumstances, dismissal of the complaint was appropriate.

FN6. The parties to this case also have disputed in their briefs and arguments before this Court the applicability of the discretionary function exception to a claim alleging that the DBS wrongfully chose not to revoke Lederle Laboratories’ license to manufacture Orimune. Neither the Court of Appeals nor the District Court specifically addressed this issue. Moreover, petitioners did not raise the issue in their petition for a writ of certiorari. We accordingly do not consider or decide the question whether the discretionary function exception bars a claim against the Government for failure to revoke a license to manufacture a polio vaccine.

A

Under federal law, a manufacturer must receive a product license prior to marketing a brand of live oral polio vaccine. See 58 Stat. 702, as amended, 42 U.S.C. § 262(a). In order to become eligible for such a license, a manufacturer must first make a sample of the vaccine product. See 42 CFR § 73.3 (Supp.1964); 21 CFR § 601.2 (1987). This process begins with the selection of an original virus strain. The manufacturer grows a seed virus from this strain; the seed virus is then used to produce monopools, portions of which are combined to form the consumer-level product. Federal regulations set forth safety criteria for the original strain, see 42 CFR § 73.110(b)(2) (Supp.1964); 21 CFR §§ 630.10(b)(2) (1987), the seed virus, see 42 CFR §§ 73.110(b)(3), (4) (Supp.1964); 21 CFR §§ 630.10(b)(3), (4) (1987), and the vaccine monopools, see 42 CFR § 73.114 (Supp.1964); 21 CFR § 630.16 (1987). Under the regulations, the manufacturer must conduct a variety of tests to measure the safety of the product at each stage of the manufacturing process. See 42 CFR §§ 73.110, 73.114 (Supp.1964); 21 CFR §§ 630.10, 630.16 (1987). Upon completion of the manufacturing process and the required testing, the manufacturer is required

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to submit an application for a product license to the DBS. See 42 CFR § 73.3 (Supp.1964); 21 CFR § 601.2 (1987).

[FN8] In addition to this application, the manufacturer must submit data from the tests performed and a sample of the finished product. Ibid.

FN7. The DBS issued a license to Lederle Laboratories to produce Orimune in 1963.

The first citation in the text is to the regulation in effect at that time. Where the regulation has remained substantially in the same form, a parallel citation is given to the current regulations. Manufacturers are required to obtain an establishment license in addition to the product license. See 42 CFR §§ 73.2-73.4 (Supp.1964); 21 CFR §§ 601.1-601.2, 601.10 (1987).

Petitioners have not challenged the issuance of an establishment license to Lederle Laboratories.

FN8. In 1972, the DBS was transferred from the National Institutes of Health to the FDA and renamed the Bureau of Biologics. See 37 Fed.Reg. 12865 (1972). In 1984, the Bureau of Biologics was renamed the Office of Biologics Research and Review. See 49 Fed.Reg. 23834 (1984). The regulations have been amended accordingly.

In deciding whether to issue a license, the DBS is required to comply with certain statutory and regulatory provisions. The Public Health Service Act provides:

"Licenses for the maintenance of establishments for the propagation or manufacture and preparation of products [including polio vaccines] may be issued only upon a showing that the establishment and the products for which a license is desired meet standards, designed to insure the continued safety, purity, and potency of such products, prescribed in regulations, and licenses for new products may be issued only upon a showing that they *542 meet such standards. All such licenses shall be issued, suspended, and revoked as prescribed by …"

regulations " § 351(d), 58 Stat. 702-703, as amended, 42 U.S.C. § 262(d).

A regulation similarly provides that "[a] product license shall be issued only upon examination of the product and upon a determination that the product complies with the standards prescribed in the regulations " 42 CFR § 73.5(a) (Supp.1964); see 21 CFR § 601.4 (1987). In addition, a regulation states that "[a]n application for license shall not be considered as filed" until the DBS receives the information and data regarding the product that the manufacturer is required to submit. 42 CFR § 73.3 (Supp.1964); 21 CFR § 601.2 (1987). These statutory and regulatory provisions require the DBS, prior to issuing a product license, to receive all data the manufacturer **1962 is required to submit, to examine the product, and to make a determination that the product complies with safety standards.

[5] Petitioners’ first allegation with regard to the licensing of Orimune is that the DBS issued a product license without first receiving data that the manufacturer must submit showing how the product, at the various stages of the manufacturing process, matched up against regulatory safety standards. See App. 12-13; Brief for Petitioners 5-6. The discretionary function exception does not bar a cause of action based on this allegation. The statute and regulations described above require, as a precondition to licensing, that the DBS receive certain test data from the manufacturer relating to the product's compliance with regulatory standards. See § 351(d), 58 Stat. 702-703, as amended, 42 U.S.C. § 262(d) (providing that a license shall issue "only upon a showing" by the manufacturer); 42 CFR § 73.3 (Supp.1964); 21 CFR § 601.2 (1987) (providing that application for license shall be deemed as filed only upon receipt of relevant test data).

The DBS has no discretion to issue a license without first receiving the required test data; to do so would violate a specific statutory *543 and regulatory directive. Accordingly, to the extent that petitioners’ licensing claim is based on a decision of the DBS to issue a license without having received the required test data, the discretionary function exception imposes no bar.

Petitioners’ other allegation regarding the licensing of Orimune is difficult to describe with precision. Petitioners contend that the DBS licensed Orimune even though the vaccine did not comply with certain regulatory safety standards. See App. 12; Brief for
Petitioners 4-6. [FN9] This charge may be understood in any of three ways. First, petitioners may mean that the DBS licensed Orimune without first making a determination as to whether the vaccine complied with regulatory standards. Second, petitioners may intend to argue that the DBS specifically found that Orimune failed to comply with certain regulatory standards and nonetheless issued a license for the vaccine’s manufacture. Third, petitioners may concede that the DBS made a determination of compliance, but allege that this determination was incorrect. Neither *544 petitioners’ complaint nor their briefs and argument before this Court make entirely clear their theory of the case.

FN9. Petitioners point to two specific regulatory standards that the product allegedly failed to satisfy. First, petitioners claim that an original virus strain from which the vaccine was made did not comply with the requirement that the strain be “free of harmful effect upon administration in the recommended dosage to at least 100,000 people susceptible to poliomyelitis.” 42 CPR § 73.110(b)(2)(i) (Supp.1964); see 21 CPR § 630.10(b)(2)(i) (1987). Second, petitioners assert that the strain, a seed virus, a vaccine monopool, and the ultimate vaccine product failed to comply with the regulatory scheme’s neurovirulence requirement. See 42 CPR §§ 73.110(b)(2)(ii), 73.110(b)(4), 73.114(b)(1) (Supp. 1964); 21 CPR §§ 630.110(b)(2)(ii), 630.110(b)(4), 630.16(b)(i) (1987). Neurovirulence is the capacity of an infectious agent to produce pathologic effects on the central nervous system. In this context, it refers to the vaccine’s ability to cause paralytic poliomyelitis. The neurovirulence of a vaccine product is tested by injecting the product into monkeys. The product meets the neurovirulence criterion only if a specified number of the animals survive and a “comparative analysis” demonstrates that the neurovirulence of the vaccine product "does not exceed" the neurovirulence of a reference product previously selected by the agency. 42 CPR § 73.114(b)(1)(iii) (Supp.1964); 21 CPR § 630.16(b)(i)(iii) (1987).

[FN10] Petitioners’ claim, if interpreted as alleging that the DBS licensed Orimune in the absence of a determination that the vaccine complied with regulatory standards, therefore does not challenge a discretionary function. Rather, the claim charges a failure on the part of the agency to perform its clear duty under federal law. When a suit charges an agency with failing to act in accord with a specific mandatory directive, the discretionary function exception does not apply.

FN10 Even the Government conceded at oral argument that the DBS has no discretion to issue a product license without an examination of the product and a determination that the product complies with regulatory standards. The transcript reads:
"QUESTION: [Supposing the DBS] did not make any examination of the application at all, or any determination other than some papers have been filed and I will now issue the license. Would that comply with the regulation?"
"[COUNSEL]: No, it would not comply with the regulation.
"QUESTION: It would violate a mandatory duty..., wouldn't it?"
"[COUNSEL]: In the extreme instance you are talking about ..., it would definitely violate that regulation."
Tr. of Oral Arg. 34-35.

[8] If petitioners' claim is that the DBS made a
determination that Orimune complied with regulatory standards, but that the determination was incorrect, the question of the applicability of the discretionary function exception requires a somewhat different analysis. In that event, the question turns on whether the manner and method of determining compliance with the safety standards at issue involve agency judgment of the kind protected by the discretionary function exception. [FN11] Petitioners contend that the determination involves the application of objective scientific standards, see Brief for Petitioners 16-17, whereas the Government asserts that the determination incorporates considerable "policy judgment," Brief for United States 36. In making these assertions, the parties have framed the issue appropriately; application of the discretionary function exception to the claim that the determination of compliance was incorrect hinges on whether the agency officials making that determination permissibly exercise policy choice. The parties, however, have not addressed this question in detail, and they have given us no indication of the way in which the DBS interprets and applies the regulations setting forth the criteria for compliance. Given that these regulations are particularly abstruse, we hesitate to decide the question on the scanty record before us. We therefore leave it to the District Court to decide, if petitioners choose to press this claim, whether agency officials appropriately exercise policy judgment in determining that a vaccine product complies with the relevant safety standards.

FN11. As noted, see n. 9, supra, the regulatory standards that petitioners claim were not satisfied in this case are the neurovirulence criterion and the requirement that virus strains be free from harmful effect. The question presented is thus whether the determination that a vaccine product complies with each of these regulatory standards involves judgment of the kind that the discretionary function exception protects.

B

The regulatory scheme governing release of vaccine lots is distinct from that governing the issuance of licenses. The former set of regulations places an obligation on manufacturers to examine all vaccine lots prior to distribution to ensure that they comply with regulatory standards. See 21 CFR § 610.1 (1978). [FN12] These regulations, however, do not impose a corresponding duty on the Bureau of Biologics. Although the regulations empower the Bureau to examine any vaccine lot and prevent the distribution of a noncomplying lot, see 21 CFR § 610.2(a) (1978), they do not require the Bureau to take such action in all cases. The regulations generally allow the Bureau to determine the appropriate manner in which to regulate the release of vaccine lots, rather than mandating certain kinds of agency action. The regulatory scheme governing the release of vaccine lots is substantially similar in this respect to the scheme discussed in United States v. Varig Airlines, 467 U.S. 797. 104 S.Ct. 2755. 81 L.Ed.2d 660 (1984).

FN12. The citation is to the regulation in effect at the time Lederle Laboratories released the lot of Orimune containing Kevan Berkowitz's dose. None of the regulations governing the release of vaccine lots has changed significantly since that time. The current regulations dealing with this subject have the same title and section numbers as the regulations cited in the text.

[9] Given this regulatory context, the discretionary function exception bars any claims that challenge the Bureau's formulation of policy as to the appropriate way in which to regulate the release of vaccine lots. Cf. id., at 819-820, 104 S.Ct., at 2767-2768 (holding that discretionary function exception barred claim challenging FAA's decision to establish a spot-checking program). In addition, if the policies and programs formulated by the Bureau allow room for implementing officials to make independent policy judgments, the discretionary function exception protects the acts taken by those officials in the exercise of this discretion. Cf. id., at 820, 104 S.Ct., at 2767-2768 (holding that discretionary function exception barred claim that employees charged with executing the FAA's spot-checking program made negligent policy judgments respecting the proper inspection.
The discretionary function exception, however, does not apply if the acts complained of do not involve the permissible exercise of policy discretion. Thus, if the Bureau's policy leaves no room for an official to exercise policy judgment in performing a given act, or if the act simply does not involve the exercise of such judgment, the discretionary function exception does not bar a claim that the act was negligent or wrongful. Cf. Indian Towing Co. v. United States, 350 U.S., at 69, 76 S.Ct., at 126-127 (holding that a negligent failure to maintain a lighthouse in good working order subjected the Government to suit under the FTCA even though the initial decision to undertake and maintain lighthouse service was a discretionary policy judgment).

[10] Viewed in light of these principles, petitioners' claim regarding the release of the vaccine lot from which Kevan Berkovitz received his dose survives the Government's motion to dismiss. Petitioners allege that, under the authority granted by the regulations, the Bureau of Biologics has adopted a policy of testing all vaccine lots for compliance with safety standards and preventing the distribution to the public of any lots that fail to comply. Petitioners further allege that notwithstanding this policy, which allegedly leaves no room for implementing officials to exercise independent policy judgment, employees of the Bureau knowingly approved the release of a lot that did not comply with safety standards. See App. 13; Brief for Petitioners 20-21; Reply Brief for Petitioners 15-17. Thus, petitioners' complaint is directed at a governmental action that allegedly involved no policy discretion. Petitioners, of course, have not proved their factual allegations, but they are not required to do so on a motion to dismiss. If those allegations are correct—that is, if the Bureau's policy did not allow the official who took the challenged action to release a noncomplying lot on the basis of policy considerations—the discretionary function exception does not bar the claim. [FN13] Because petitioners may yet show, on the basis of materials obtained in discovery or otherwise, that the conduct challenged here did not involve the permissible exercise of policy discretion, the invocation of the discretionary function exception to dismiss petitioners' lot release claim was improper.

FN13. The Government's own argument before this Court provides some support for petitioners' allegation regarding the Bureau's policy. The Government indicated that the Bureau reviews each lot of vaccine and decides whether it complies with safety standards. See Tr. of Oral Arg. 42. The Government further suggested that if an employee knew that a lot did not comply with these standards, he would have no discretion to approve the release of the lot. See id., at 31-32.

IV

For the foregoing reasons, the Court of Appeals erred in holding that the discretionary function exception required the dismissal of petitioners' claims respecting the licensing of Orimune and the release of a particular vaccine lot. The judgment of the Court of Appeals is accordingly reversed, and the case is remanded for further proceedings consistent with this opinion.

It is so ordered.

108 S.Ct. 1954, 486 U.S. 531, 100 L.Ed.2d 531, 56 USLW4549

Briefs and Other Related Documents (Back to top)

• 1988 WL 1026266 (Appellate Brief) Reply Brief for Petitioners (Apr. 12,1988)
• 1988 WL 1031653 (Appellate Brief) Reply Brief for Petitioners (Apr. 12, 1988)
• 1988 WL 1026265 (Appellate Brief) Brief for the United States (Mar. 29, 1988)
• 1988 WL 1031651 (Appellate Brief) Motion for Leave to File Brief as Amicus Curiae and Brief for Lederle Laboratories, a Division of American Cyanamid Co. as Amicus Curiae in Support of Respondent (Mar. 28, 1988)
• 1988 WL 1031652 (Appellate Brief) Brief for the United States (Mar. 28, 1988)
Appendix A
Reviewer’s General References From Before 2006

108 S.Ct. 1954
100 L.Ed.2d 531, 56 USLW 4549
(Cite as: 486 U.S. 531, 108 S.Ct. 1954)

• 1988 WL 1026263 (Appellate Brief) Brief for Petitioners (Feb. 25, 1988)

• 1987 WL 881024 (Appellate Brief) Brief for the United States (Dec. 11, 1987)

• 1987 WL 881025 (Appellate Brief) Brief for Petitioners (Oct. Term 1987)

END OF DOCUMENT
EXHIBIT 1:

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Sent At: 12:23 –0400
On: 7/27/06

E-mail's Text

To: eric.fombonne@mcgill.ca
From: "Paul G. King" <drking@gti.net>
Subject: PervasiveDevelopmentalDisordersinMontreal,Quebec,Canada_Prevalence and Links With Immunizations PEDIATRICS 2006_118(1)_e139-e150
Cc:
Bcc: *********************************************
References:

Dear Dr. Fombonne,

I read your important paper with interest as I have been asked to critically assess your paper and to formally report my findings appropriately.

You could greatly facilitate my endeavors if you could provide me with a tabulation of:
a) the number of students enrolled and b) the total number of PDD cases in each grade -- so that I might verify the values you reported for the incidence rates for each grade.

In return for your assistance not only would I include you as a helpful reference in my review of your paper but would also provide you with a draft for your review and comment before, if possible, submitting it for publication.

To provide you with adequate time to respond to any concerns you may have with my draft, could you provide this information as soon as possible because I am working on a submission deadline and may be forced to proceed without it.

Thanking you in advance for your valuable assistance in this matter, I remain

Respectfully yours,

Paul G. King, PhD
President
Paul G. King Consulting
A CONFIDENTIAL Consultancy in Chemistry and Pharmaceutics
EXHIBIT 2:

To: eric.fombonne@mcgill.ca  
Sent At: 08:51 –0400  
On: 8/18/06

Dear Dr. Fombonne,

As my previous email to you on 27 July indicated, I read your important paper with interest as I have been asked to critically assess your paper and to formally report my findings appropriately.

As I said previously, you could greatly facilitate my endeavors if you could provide me with a tabulation of:

a) the number of students enrolled (registered) in each grade, and

b) the total number of PDD cases in each grade --

so that I might verify the values you reported for the incidence rates for each grade because, as I communicated to your assistant when we spoke on the telephone on Wednesday, 16 August 2006, if you fail to respond by 23:59:59 EDST on Monday, 21 August 2006 with the information I have requested, your inaction will compel me to proceed with submitting the draft for review and then publication with the notation that you declined to respond to my emails (copies of the first email and this last email will be included in my draft submission) and telephone calls to your office even though you were informed that there were significant data discrepancies (e.g., your reporting of 61 "autistic disorder" cases in 3 places in your paper but reporting 60 "autistic disorder" cases in another place) in the values your article reported as well as other apparent fundamental study problems that seemingly, you see no need to address.

Hopefully, after receiving this third email and reviewing the detailed messages I left for you including those left with your assistant, you will respond with the needed values BEFORE the Tuesday, 22 August 2006.

Respectfully yours,

Paul G. King, PhD
President
Paul G. King Consulting
A CONFIDENTIAL Consultancy in Chemistry and Pharmaceutics
1. Dr. Gary S. Goldman’s Comments:

“Delivered-To: drking@gti.net
Date: Fri, 04 Aug 2006 04:52:48 -0400
From: pearblossominc@aol.com
Subject: Analysis of Fombonne’s manuscript...
To: drking@gti.net

Dear Dr. King,

Your analysis of the Fombonne paper is certainly much different from the approach I would have taken--my evaluation would have been 1 to 2 pages at most emphasizing the following key points:

1. First, if the vaccination schedule and levels of Thimerosal do not accurately reflect what was actually administered to the children, then this needs to be corrected upfront. I do not believe that a level of Thimerosal level can go to "nil" suddenly one year--especially due to the fact that (1) it is likely that existing stock would be utilized and (2) patients that had already been vaccinated according to a previous vaccination schedule would likely have follow through with the administering of final vaccine doses according to their previous vaccination schedule. All sources of Thimerosal need to be accounted for, and Dr. King, you indicate that the author perhaps did not consider all these sources (for example impact of flu vaccine, etc). This is a fundamental problem before even proceeding with further analysis.” [Reviewer’s note: Hepatitis B vaccine is the other Thimerosal-preserved vaccine that was not discussed.]

“2. It appears that there were several periods during which the vaccination schedule changed. You cannot model outcomes using means of 3 consecutive grade levels (3 different ages of students) when you are attempting to analyze trends in the vaccination schedule that occurred or changed during 1 given year. This produces ‘fuzzy’ outcomes.

3. At the year of any given change in the vaccination schedule, especially when a vaccine has been added to the schedule, there is automatically an expectation of a linear increase in adverse outcomes since as vaccination progresses each successive year following a given change in a vaccination schedule, the vaccine coverage linearly increases (assuming stable annual population). For example, each year a new cohort of vaccinees enters the group being inspected, it contributes to the linear increase in PDD-rates until the age group under consideration has reached saturation--with all children finally having received the added vaccine --at which point the curve of PDD-rates (or adverse reactions in general) will naturally level off.

4. I would like to call you and discuss Figure 1 MMR vaccine coverage and PDD rates over time. It appears that the MMR coverage was 91 to 100% (in other words, high), so as a rough assessment, one could consider all students had received this vaccine. When using ‘prevalence’ of PPD instead of ‘incidence’ of PPD, the analysis gets tricky!!! Since, as we consider increasingly older age groups, more and more PPD-diagnosed individuals would tend to accumulate in these age categories when ‘prevalence’ is the standard of measure. When did MMR vaccine begin in the study community? I am not certain what Figure 1 is showing, but there appears to be a roughly an increase from about 30 per 10,000 to 100 per 1000 from year of birth 1987 to 1994/1996???

If MMR vaccine started at year of birth 1988 (since I do not see a data point for MMR coverage for 1987), then we would expect precisely what has been plotted. As each successive cohort of MMR-vaccinated children was added each year to the population, we would expect PPD-rates to roughly increase linearly and then level off (year of birth 1994 to 1996 might reflect such a leveling off) at a higher level. Again, such trends or associations between vaccination and PDD-rates are often temporal--meaning they do not precisely coincide strictly with vaccination practices, but are delayed or offset by time of diagnoses.

5. Figure 2 could also reflect temporal relationships between thimerosal and diagnoses of PDD. More years would be necessary following year of birth 1996-1998 since there could be a delay of more than 3-years before the PDD rate became effectively lower.

To go any further with the evaluation of this paper--given the major problems inherent in item #1, and the complicating factors shared in items #2 and #3, would not be meaningful in my opinion. The authors have obviously not provided a proper methodological framework for which to make the conclusions that they make and, as an evaluator, any comments beyond those given above would only be conjecture. In summary, for the author to perform the analysis properly, data consisting of date of birth should be utilized, not grades, and the data need to be tallied by age--rather than using the mean of 3-combined grade levels since the this averaging approach is not sensitive enough to the abrupt changes that occurred in the vaccination schedule.

Sincerely,
Gary S. Goldman, Ph.D."

Critical References Cited:

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Appendix C
Other References and Comments


2. The Geiers’ Comments:

“Delivered-To: drking@gti.net
From: mgeier@comcast.net
To: drking@gti.net
Subject: Dr. Geier has read your analysis of Fombonne
Date: Tue, 22 Aug 2006 03:49:40 +0000

Dear Dr. King,
I have read you analysis of the paper of Fombonne article recently published in Pediatrics. I did not see any errors and I found your analysis unique and very effective. I look forward to your publication of this analysis and I look forward to a response by Dr. Fombonne addressing the serious errors in the paper which you have pointed out. Basically, I think his Canadian data is supportive of the trends relating Thimerosal levels and the rate of ASDs which we have published and which have also been published by CDC.
Dr. Mark Geier”

[Note: Mark Geier says in one of his papers/broadcasts that the autism rate for boys from the time they made hepB with thimerosal mandatory at birth until 1999 (when thimerosal was putatively removed), I believe the time frame was boys born between 1996-1999, the incidence of ASD boys in that population is between 1:30 and 1:40. That's right, about 2.5 to about 3.33 percent of all boys born between 1996 and 1999. Source: Email: “Coleman” at 13:50 on 8/4/06 –0400 responding to: [EOHarm] Re: for newspaper article-current rate of autism i.]


“EPIDEMIOLOGY OF MUMPS IN QUEBEC, 1970-1995

In 1995, as part of its measles control programs, the National Advisory Council on Immunization recommended the use of the trivalent measles-mumps-rubella vaccine (MMR) for the second measles vaccination (1). However, the Mumps and Rubella Consensus Conference demonstrated that mumps are considered a very low-priority disease in Canada and a single-dose vaccination program seems acceptable (2). Since the need for a second dose of mumps vaccine is questionable, a review of the recent epidemiology of mumps may be useful. …

EPIDEMIOLOGY OF MUMPS IN QUEBEC, 1970-1995

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Data on vaccination coverage and from a number of files containing epidemiologic data, from 1970-1995 in Quebec, are presented in this report.

Vaccination coverage

The mumps vaccine was included in the regular childhood vaccination program in Quebec in 1976, following approval of the trivalent MMR vaccine. There has been no extensive study of vaccination coverage for all birth cohorts since 1970. Therefore, vaccination coverage has been estimated by a summary of data from transverse studies of vaccination coverage reported in the province. Figure 1 shows that vaccination coverage rose rapidly after 1976 and has remained at or above 95% since 1980.

Epidemiologic data

Quebec has three sources of information on the epidemiology of mumps a notifiable diseases surveillance system (MADO), a computerized hospitalization file (Med-Écho) which was introduced in 1981, and the Canadian Virus Surveillance Program (CVSP) which began in 1970.

MADO

Although mumps did not become a notifiable disease until 1986, the provincial ministry of health has collected data on this disease from 1970-1995 with the exception of 1984 and 1985 (Table 1).
Appendix C
Other References and Comments

Figure 1 Vaccination coverage for mumps vaccine by birth cohort, 1973-1990

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* data to 31 March 1995

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Appendix C
Other References and Comments

Between 1980 and 1985, a single major epidemic was reported. This epidemic, which involved 440 cases, occurred between November 1988 and July 1989 in Rivière-du-Loup and vicinity, in the Lower St. Lawrence region. All the cases reported to the public-health unit met the standard clinical definition of parotitis persisting at least 2 days. The index case was a 13-year-old boy who developed parotitis in early November 1988, with the diagnosis of mumps being confirmed by serology. He attended a secondary school with 1,682 students with 48% vaccination coverage before the beginning of the epidemic. Following serologic confirmation of the index case, a vaccination campaign was undertaken and 632 students received the MMR vaccine, for an overall coverage of 85%.


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<tr>
<td>Target</td>
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### 3. General National Goals and Targets

- Ensure that all vaccines to be administered have been properly transported, stored, and delivered and that there is continual surveillance for adverse reactions and monitoring of vaccine efficacy.
- Review all goals and targets in 1999.

#### 3.1 Diphtheria

**Goal**

- Eliminate indigenous cases of diphtheria by the year 1997.

**Targets**

- Achieve and maintain up-to-date diphtheria immunization by the second birthday in 97% of children by the year 1997.
- Achieve and maintain up-to-date diphtheria immunization by the seventh birthday in 99% of children by the year 1997.

#### 3.2 Invasive *Haemophilus influenzae* type b infections Goal

- Achieve and maintain the absence of preventable cases of invasive *Haemophilus influenzae* type b (Hib) infections in children by the year 1997.

**Target**

- Achieve and maintain up-to-date Hib immunization by the second birthday in 97% of children by the year 1997, recommending that the immunization be given in accordance with the recommended schedule beginning at 2 months of age.
Appendix C
Other References and Comments

3.3 Hepatitis B

Goal
- Reduce the prevalence of indigenously acquired chronic hepatitis B infections in children and young adults by 90% by the year 2015.

Targets
- Screen 100% of pregnant women for evidence of hepatitis B surface antigen and immunize 100% of neonates of carrier mothers with vaccine and hepatitis B immune globulin as soon as possible after birth, by the year 1995.
- Establish routine universal hepatitis B immunization for children by the year 1997.
- Achieve and maintain 95% hepatitis B immunization of populations targeted in universal programs by the year 1997.
- Ensure that each province and territory has a policy to provide hepatitis B vaccine to all high-risk groups as outlined in the Canadian Immunization Guide by the year 1995.

3.4 Measles

Goal
- Eliminate indigenous measles in Canada by the year 2005.

Targets
- Achieve and maintain measles immunization with the first dose of vaccine by the second birthday in 97% of children by the year 1997.
- Achieve and maintain measles immunization with a second dose by the seventh birthday in 99% of children by the year 2000.
- Achieve and maintain an incidence of less than 1 per 100,000 population in each province and territory by the year 2000.

3.5 Mumps

Goal
- Maintain an active prevention program for mumps to minimize serious sequelae.

Targets
- Achieve and maintain mumps immunization by the second birthday in 97% of children by the year 1997.
- Achieve and maintain mumps immunization by the seventh birthday in 99% of children by the year 1997.

3.6 Pertussis

Goals
- Reduce the morbidity and mortality related to pertussis infection.
- Immunize all Canadian children against pertussis according to NACI guidelines.

Targets
- Achieve and maintain up-to-date pertussis immunization by the second birthday in 95% of children by the year 1997.
- Achieve and maintain up-to-date pertussis immunization by the seventh birthday in 95% of children by the year 1997. Have all reported cases of pertussis managed appropriately.
- Ensure that severity of disease, as indicated by pertussis-related admissions to intensive care units, is reduced by 50% by the year 1997 (based on a moving average).
- Ensure that reporting of pertussis cases to the national level is standardized by the year 1994.

3.7 Poliomyelitis

Goals
- Maintain the elimination of wild indigenous poliomyelitis.
- Prevent future import-related cases.

Targets
- Achieve and maintain 97% immunization with three doses of polio vaccine by the second birthday by the year 1997.
Appendix C
Other References and Comments

- Achieve and maintain up-to-date poliomyelitis immunization by the seventh birthday in 99% of children by the year 1997.

3.8 Rubella

Goal
- Eliminate indigenous rubella infection during pregnancy and thus prevent fetal damage, congenital rubella syndrome, and other negative outcomes of infection by the year 2000.

Targets
- Achieve and maintain up-to-date rubella immunization by the second birthday in 97% of children by the year 1997.
- Achieve and maintain up-to-date rubella immunization before school entry in 99% of children by the year 1997.
- Achieve and maintain up-to-date rubella immunization in 99% of 14- to 15-year-olds by the year 1997.
- Screen serologically and/or obtain date of immunization of ALL pregnant women seen prenatally for rubella susceptibility by the year 1995.
- Achieve and maintain postpartum immunization for rubella of 99% of all susceptible women prior to hospital discharge by the year 1995.
- Ensure that all women of childbearing age have a documented history of rubella immunization and, if not, that they are offered rubella vaccine to decrease the rate of rubella-negative primigravida women to less than 4% by the year 1997.

3.9 Tetanus

Goal
- Maintain absence of neonatal and childhood tetanus.

Targets
- Achieve and maintain up-to-date tetanus immunization by the second birthday in 97% of children by the year 1997.
- Achieve and maintain up-to-date tetanus immunization by the seventh birthday in 99% of children by the year 1997.

In addition to the above goals and targets, consensus conferences have stressed the need:
- to follow the recommendations from the working group on polio eradication and from the national certification commission;
- to reinforce the importance of adult immunization for the above-mentioned diseases (tetanus in particular);
- to achieve vaccine coverage levels at the national, provincial, territorial and local health-unit levels; and
- to try to immunize at the age recommended by NACI.

Draft national guidelines for childhood immunization practices are being developed and will be published by LCDC. Adherence to these guidelines should help Canada achieve these goals and targets in the future. Beyond endorsement at the national, provincial, and territorial levels and by professional organizations, everyone should work toward achieving these goals and targets for a better future for our children. As can be seen in the later sections of this report, serious efforts need to be made to achieve some goals and targets, although some have been already achieved and good progress is being made for some others. Achieving the disease-reduction target for pertussis will not be possible without replacing the current whole-cell vaccine with more efficacious and acceptable (less reactogenic) new acellular vaccines. Evaluation will be the key to monitoring progress toward the achievement of the goals; then corrective action can be taken as needed. Many evaluation tools remain to be put in place at national, provincial, territorial, and local levels.”