mercury in RhoGam

HREF="http://www.fda.gov/cber/blood/mercplasma.htm">http://www.fda.gov/cber/blood/mercplasma.htm</A>

Mercury in Plasma-Derived Products
[<A HREF="http://www.fda.gov/cber/vaccine/thimerosal.htm">Thimerosal in Vaccines</A>]

This is the second update of the original posting. The Ortho-Clinical Diagnostics product, Rho (D) Immune Globulin (Human), RhoGAM, was originally listed as containing 9 milligrams of mercury in each dose. The first update indicated that the correct amount is 9 micrograms. In this second update additional information is included regarding different doses of RhoGAM, and the mercury content of other Rho (D) Immune Globulin products is described.

The EPA has recently raised concerns regarding mercury exposure. These concerns have been in the context of chronic exposure to methyl mercury in milligram amounts. In contrast, plasma-derived products (except anti-venoms) containing ethyl mercury are usually given as one or two injections. Furthermore, the ethyl mercury content of these products is in the form of a preservative, thimerosal, which breaks down to form ethyl mercury in microgram amounts.

In the past, products made in multiple-use vials, e.g. Immune Globulin (Human), used for Hepatitis A prophylaxis, contained a preservative, such as ethyl mercury-containing thimerosal, to avoid contamination. These were older products and most of them have been discontinued.

Rho (D) Immune Globulin (Human) products are as follows:

RhoGAM, Ortho Clinical Diagnostics
BayRho, Bayer

WinRho, Cangene

RhoGAM [licensed 1968]

On April 16, 2001, Ortho Diagnostics was approved by FDA to produce RhoGAM without thimerosal, and at that time, Ortho agreed to distribute only thimerosal-free product to the US market. The product has a 2-year dating period, so that material released before April 16, 2001 may still be on the market. The package insert for RhoGAM containing thimerosal (i.e., for those lots manufactured prior to April 2001) does state that this product contains thimerosal. However, there is no warning in the package insert related to thimerosal or mercury content.

Regarding the total thimerosal content of the previously released RhoGAM, the product was manufactured in two doses only: the standard dose of "300 micrograms" of anti-D, and the micro-dose of "50 micrograms" of anti-D. The fill volume for both the standard dose and micro-dose products is typically between 0.6 and 0.8 mL. Preservative-containing RhoGAM contains thimerosal at 0.003%, or 30 micrograms per milliliter. Thimerosal is about 50% ethyl mercury by weight. Hence, a patient receiving a dose of RhoGAM (0.7 ml on average) will have received 10.5 microgram of ethyl mercury.

There are three indications for which an Rh-negative pregnant woman would receive a significantly larger dose of RhoGAM: a fetal-maternal hemorrhage early in the pregnancy, a fetal-maternal hemorrhage greater than 15 ml of Rh+ red cells, and an Rh+ transfusion. In the first case, a single 300 microgram dose of RhoGAM, is recommended at 12-week intervals. For the second two indications, a procedure exists by which to determine the dose of RhoGAM required, based on the amount of Rho+ red cells in the maternal circulation: the Kleihauer-Betke elution test (see the AABB Technical Manual, 13th ed., pp. 507-8.) The total

dose of mercury received can be calculated by multiplying the number of RhoGAM
syringes administered by 10.5 micrograms.

BayRho [licensed 1971]

The Bayer Corporation makes a Rho (D) Immune Globulin product (BayRho) which in the past contained thimerosal; this product has been manufactured without preservative since 1996, so that no in-date BayRho contains thimerosal. Regarding the previously distributed product, the volume of a single dose of the
Bayer product was approximately 0.7 ml. The thimerosal concentration was 0.01%, so
the total mercury in a single dose would have been approximately 35 micrograms of ethyl mercury.

WinRho SD [licensed 1996]

The Cangene Corporation makes a freeze-dried Rho (D) Immune Globulin (WinRho SD); this product has never contained a preservative.

In addition, five other plasma-derived products remain on the market that contain or contained ethyl mercury preservatives. They are as follows:

Antivenin (Crotalidae) Polyvalent (Equine); Pit viper snake antivenom, Wyeth
Antivenin (Micrurus fulvius); Coral snake antivenom (Equine), Wyeth
Crotalidae Polyvalent Immune Fab (Ovine); Pit viper snake antivenom, Protherics
Antivenin (Lacrodectus mactans); Black Widow spider antivenom Equine), Merck
Lymphocyte Immune Globulin: Anti-thymocyte Globulin (Equine), Pharmacia and Upjohn

Pit Viper [Antivenin (Crotalidae) Polyvalent, licensed 1954] and
Coral Snake [Antivenin (Micrurus fulvius), licensed 1967] antivenoms by Wyeth

These products are equine antisera. They are in lyophilized form and when reconstituted contain 0.005% thimerosal (50 micrograms per milliliter). The diluent, WFI, contains the preservative phenylmercuric nitrate at 0.001%

concentration (10 micrograms per milliliter). A patient bitten by a snake may receive 15
or more vials (doses of 50 vials have been reported) if the envenomization is severe. A 15 vial dose of this antivenom would contain 4.7 milligrams of mercury.

Wyeth plans to discontinue these products; however, the current supply will last 1-2 years. Rattlesnake bites are dangerous and can cause serious morbidity
or mortality. In the interest of the public health these products need to be available until sufficient Ethyl mercury-free product can be provided to the public.

Pit Viper antivenom [Crotalidae Polyvalent Immune Fab (Ovine) licensed October 2000, Protherics]

Mercury is not added to the final product in the form of a preservative, but thimerosal is used to assure that the affinity columns used in the manufacturing of this product do not become bacterially contaminated with repeated use.
The product was approved but the Ethyl mercury content was limited to not more
than 104.5 micrograms Ethyl mercury per vial, with a recommended maximum dose of 18 vials. A patient receiving this product would receive about 1.88 milligrams of mercury.

Black Widow Spider antivenom [Antivenin (Lactrodectus mactans), licensed 1936, Merck]

This product is an equine antiserum. The reconstituted product contains 0.1 milligrams of mercury per milliliter, so that the maximum 2-vial dose would contain 0.25 milligrams of mercury. Black Widow Spider bites can be lethal, and
the dose is limited to not more than two vials. It has been determined that removal of the product from the market by the FDA would not be in the best interests of public health.

Anti-thymocyte Globulin [Lymphocute Immune Globulin, licensed 1981, Pharmacia & Upjohn]

This product is an equine immune globulin. In 1995 a thimerosal-free

formulation was approved and in 1998 thimerosal was removed from manufacturing.