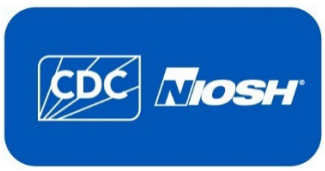
National Institute for Occupational Safety and Health

NIOSH Final Reevaluation Determination of Pertuzumab on the NIOSH List of Hazardous Drugs in Healthcare Settings

Docket Number CDC-2020-0046, NIOSH-233-C

November 5, 2024



U.S. Centers for Disease Control and Prevention
National Institute for Occupational Safety and Health

NIOSH Reevaluation of Pertuzumab on the NIOSH List of Antineoplastic and Other Hazardous Drugs in Healthcare Settings

NIOSH Decision

NIOSH has decided to remove pertuzumab from the *NIOSH List of Antineoplastic and Other Hazardous Drugs in Healthcare Settings* (the *List*) [NIOSH 2016]. NIOSH has determined that potential occupational exposures to pertuzumab are unlikely to result in systemic exposures that pose a hazard for healthcare workers based on a reevaluation of the scientific information at the manufacturer's request. Pertuzumab does not meet the NIOSH definition of a hazardous drug for healthcare workers.

Basis of the Decision

The manufacturer requested a reevaluation of pertuzumab because systemic pertuzumab concentrations associated with the toxicities of concern are unlikely to be achieved via inadvertent exposures in a healthcare settings. **Based on its reevaluation, NIOSH determined that due to the intrinsic properties of the molecule and the anticipated routes of exposure in a healthcare workplace, systemic bioavailability in healthcare workers necessary for the developmental effects of concern are unlikely.**

NIOSH has decided to remove pertuzumab from the NIOSH *List* of hazardous drugs. The hazard posed by pertuzumab during occupational exposure is minimal because pertuzumab is predicted to have low systemic bioavailability which limits the opportunity for the necessary repeated systemic exposures at a level that would cause fetal harm. Pertuzumab is expected to have very low systemic bioavailability after inhalation, dermal or oral exposure. Accidental occupational percutaneous exposures are unlikely to deliver a single sufficient dose or be repeated frequently enough to achieve a significant human dose. The lack of bioavailability and unlikelihood of employee exposure to a harmful dose will likely minimize the hazards associated with potential occupational exposure. The data on pertuzumab do not provide a no adverse effect level (NOAEL) for increased incidence of embryo-fetal lethality, renal hypoplasia, impaired renal development, amniotic fluid deficiency, or other developmental toxicities. However, a single worst case exposure would be unlikely to cause the most sensitive health effect observed, oligohydramnios, or other observed effects. For the development of oligohydramnios, a worst-case exposure would likely need to be continuous or frequently repeated throughout the second and third trimester of pregnancy. While it is possible that a worker might inhale a single worst case dose, it is highly unlikely that this would be repeated frequently enough to provide a large enough dose to cause fetal harm.

Prior NIOSH Action on Pertuzumab

NIOSH added pertuzumab to the list of hazardous drugs in 2016 [NIOSH 2016]. Pertuzumab was placed on Table 1, Antineoplastic drugs, including those with manufacturer's safe-handling guidance (MSHG), based on the American Hospital Formulary Service (AHFS) Classification 10:00, and embryo lethality, fetal effects, and oligohydramnios. Supplemental information provided in the *List* was a Black Box warning on embryo-fetal death and birth defects, and a designation as an FDA Pregnancy Category D drug.

Toxicity Evaluation

Pertuzumab is a targeted therapeutic monoclonal antibody; therefore, it does not pose the same cytotoxic, genotoxic, and carcinogenic hazard as many other antineoplastic drugs.

Carcinogenicity, Genotoxicity, Reproductive toxicity, and Organ Toxicity at Low Doses

First NIOSH considered toxic effects to determine if those effects would meet NIOSH's definition of a hazardous drug [NIOSH 2016]. Pertuzumab is a drug approved by the Center for Drug Evaluation and Research. Because pertuzumab is a protein it is not expected to be genotoxic. The International Conference on Harmonization (ICH) guidance does not require genotoxicity testing. No carcinogenicity testing or specific fertility testing was performed on pertuzumab. No adverse effects on fertility organs in males or females were observed in animal studies up to six months of exposure. No evidence was seen of organ toxicity at low doses in animal studies [Genentech 2020]. The package insert does not include any manufacture's special handling information pertaining to handling genotoxic or cytotoxic drugs.

Developmental Toxicity (Including Teratogenicity)

There is evidence from studies in cynomolgus monkeys that pertuzumab may have developmental toxicity. When evaluating potentially hazardous drugs for workers, NIOSH considers whether data suggest potential developmental effects at one human equivalent dose (HED) equivalent or lower or if data suggest potential systemic toxicological effects below 10 mg/day [NIOSH 2016].

Determining the Human Equivalent Dose (HED)

Pertuzumab caused embryo-fetal lethality in cynomolgus monkeys at exposures equal to 0.24, 0.76, and 2 times the HED as determined by area under the curve (AUC), which FDA recognized as the appropriate dose comparator [FDA 2012]. The dose comparison by AUC is more biologically appropriate than comparison by allometric scaling due to the half-life of the drug and the time between dosing.

Health Effects at Multiple Dosing Levels and Days of Gestation

The tested cynomolgus monkeys did not show signs of deactivating antibody formation, so treatment with pertuzumab was expected to be biologically relevant throughout the treatment period. Cynomolgus monkeys received a loading dose on gestational day (GD) 19 followed by 8 lower doses given at 4-to-7-day intervals up to day GD 50. Embryo-fetal lethality was dose dependent and occurred at all tested doses between GD 25-70. After caesarean section on GD 100 oligohydramnios (amniotic fluid deficiency) and discolored amniotic fluid were noted in 2 of 8 pregnancies at 0.2 times HED and in all surviving offspring at higher doses. Adverse developmental effects included increased brain size, decreased kidney size, decreased crown to rump length, and decreased hind foot length and were apparent in most surviving offspring at all doses. Microscopic evidence of renal hypoplasia and impaired renal development were seen in 100% of surviving offspring with dose related incidence from slight to marked severity. At doses greater than 0.7 times the HED there was significant dose dependent decreased lung weight.

No Observed Adverse Effect Level (NOAEL)

There was no tested level at which no effects were seen in the developmental toxicity study. The lowest systemic dose in a monkey at which exposure to pertuzumab is demonstrated to cause developmental toxicities in the offspring of pregnant animals is 10 mg/kg/dose following a 30 mg/kg loading dose (see Table 1). This is the lowest tested dose and is equivalent to 0.24 times the human dose (by AUC) of 420 mg administered every 3 weeks, or 4.8 mg/day (420 mg/21 days x 0.24). There is no established NOAEL.

Observed Fetal Death

FDA [2012] stated in the Pharmacology review “Beginning on GD 25 fetal lethality was observed at doses greater than or equal to 30/10 mg/kg [30 mg/kg initiation dose/10 mg/kg follow-up doses] (31% lower than the expected exposure in humans after IV administration at therapeutic doses, by AUC). Fetal effects were also noted at doses greater than or equal to 30/10 mg/kg. Malformations were observed at both the 100/33.3 and the 150/100 mg/kg dose levels; the latter dose level provides exposure which is approximately 2-fold greater than expected therapeutic doses in patients, based on AUC.”

Mechanism of Pharmacologic Action

Decreased amniotic fluid, oligohydramnios, is suggested to be a result of pertuzumab activity leading to delayed renal development in the fetus, not due to effects in the mother, so the exposure to the fetus is important to consider. Work from Wang et al. [2016] suggests that in monkeys in the first trimester of pregnancy there is a low level of IgG (a different IgG than pertuzumab) placental transfer, with less than 1% (0.73%) of maternal serum concentration levels transferred to fetal serum at GD 50. The amount transferred between maternal blood stream and fetal blood increases over time, reaching as high as 80% of the maternal level at GD 139. This finding is similar to those from other studies with other IgG forms. In Breslin et al. [2015] a different IgG was found to be at 0.6% (0.006 ratio) of maternal monkey serum concentration in monkey fetal tissues at gestational day 50. Moffat et al. [2014] found similarly low concentrations of IgG transfer at GD 50 in monkeys, 0.2% of maternal serum concentration. They also found similarly low levels of fetal IgG transfer in rats early in pregnancy, rising late in pregnancy (0.2–0.3% at GD 13 and 10–15% at GD 21). This is consistent with the current models of neonatal Fc-Receptor (FcRn) binding mediated antibody transfer across the placental barriers, where later increased expression of the FcRn as gestation progresses leads to increased transport of IgGs across the

placental barrier. In humans it appears that little IgG is transferred across the placenta until after 13–16 weeks gestation, with fetal levels of IgG being between 5%-10% in the period between 17- and 22-weeks gestation.

This means that the relevant fetal exposure early in pregnancy is low during early development, when oligohydramnios may first develop and lead to malformation and other developmental issues but would increase greatly later in pregnancy.

Fetal exposure in Genentech's embryo-fetal development study was also likely less than 1% of maternal exposure levels, which were at the 0.24 human expected therapeutic exposures in the low (30/10 mg/kg) dose groups, early in fetal development [FDA 2012]. Despite fetal exposure reaching levels Genentech reports at 2.5 times human therapeutic exposures (by body weight, not AUC) at cesarean section, early fetal exposure in affected groups was likely much lower, so the exposure levels earlier in the pregnancy, which were likely lower than those estimated at the end of pregnancy, could be responsible for the observed developmental effects.

Trastuzumab as a Model for Human Exposure During Pregnancy

Cases of oligohydramnios have been reported for patients treated with another monoclonal antibody, which also targets HER2, trastuzumab. In one case [Watson et al. 2005], treatment with trastuzumab continued through 23 weeks of gestation. In the weeks following the cessation of treatment, as serum levels of trastuzumab decreased, amniotic fluid index increased. A review [Zagouri et al. 2013] of the available literature concerning Trastuzumab (Herceptin™) use during pregnancy shows that exposure during just the first trimester had babies born with no complications, with no deaths or oligohydramnios. There was a trend of increased incidence in oligohydramnios with increased exposure to trastuzumab. In the available studies, it appears that trastuzumab related oligohydramnios was reversible following cessation of treatment, as seen in the Watson et al. [2005] case, with generally good outcomes for the fetus. This indicates that a continuous exposure to trastuzumab is likely a necessary condition to create and maintain the renal insufficiency in the fetus that leads to oligohydramnios and the resulting fetal growth limitation and malformations. This would likely be true also of pertuzumab, given the two similar mechanisms of action. In humans, this would require repeated intravenous treatment.

In summary, the evidence indicates that for pertuzumab to pose a developmental hazard, systemic exposures, regularly repeated, of 10 mg/day or systemic human therapeutic doses would be required.

Hazard Characterization

Large protein molecules

Characterizing the occupational hazard posed by large molecules used as drugs (for example, monoclonal antibodies such as pertuzumab), in healthcare settings is challenging. Therapeutically, monoclonal antibodies are delivered intravenously. Studies conducted for the therapeutic efficacy and safety of monoclonal antibodies have also used intravenous exposures. No oral, inhalation, or dermal exposure studies of therapeutic monoclonal antibodies have been conducted because these therapies are not typically delivered via these routes.

NIOSH evaluated the routes of exposure and the associated potential hazards of pertuzumab. However, quantitative data on the bioavailability of pertuzumab specifically or monoclonal antibodies generally through routes of exposure other than IV are limited. There are also few case studies of human in utero exposures to pertuzumab, though some data is available relating to pregnant women being treated with a monoclonal antibody with a similar mechanism of action, trastuzumab.

Inhalation exposure and bioavailability

The most potentially relevant routes of occupational exposure for pertuzumab are inhalation and injection. The human recommended dose of pertuzumab is 420 mg per 3-weeks [Genentech 2020]. This is equivalent to a daily dose of 20 mg/day (420mg/21 days). As previously indicated, inhalation bioavailability of large molecules like immunoglobulins and monoclonal antibodies (e.g., pertuzumab) is likely less than 5% [Pfister et al. 2014]. Inhalation exposure would require inhalation of a dose equivalent to 20 mg/day each day over several weeks. In workers exposed by inhalation, NIOSH estimates that only 5% of the exposure would be systemically available. Exposure to a full human dose via inhalation would require inhalation of 20 mg/day each day for several weeks and lead to systemic exposure 0.05 times that of the treated patient. While the associated health effect has no NOAEL, the lowest tested dose that led to developmental effects in monkeys was 0.2 times that of HED by AUC. Still, inhalation of 20 mg/day on a single day would be unlikely. The chance of repeated inhalation of this dose each day over weeks is very unlikely. A molecule of this size will not easily reach air concentrations that would allow such exposures (2 mg/m^3 in air). This molecule is not a volatile compound, so inhalation exposures would be to dusts or droplets. It is unlikely that there would be many instances in healthcare workplaces where large enough volumes of dusts or droplets would be generated that would result in airborne concentrations that reach human recommended dose. Inhalation exposures to a full human recommended dose would still, due to limited bioavailability, result in much lower effective systemic exposure. NIOSH criteria in the *Procedures for the Developing the NIOSH List* state that adverse effects below the maximum human recommended dose generally support inclusion on the NIOSH *List*. Inhalation exposure of a maximum human recommended dose would not be sufficient to cause a systemic exposure high enough to cause a developmental effect.

Percutaneous exposure

At the highest concentration provided 30 mg/mL (420 mg/14 mL) an accidental injection would require a nearly 670 μl injection to achieve a human dose. A needle stick may deliver less than a μl of fluid, not the several hundred needed for a human dose [Gaughwin 1991; Krikorian et al. 2007]. A needle stick of the required volume to achieve a toxic dose is unlikely. Additionally, because the oligohydramnios, and related effects, are reversible these levels of exposure would need to be consistently repeated throughout the second and third trimester of pregnancy, not just the result of a single workplace accident. In workers, exposures of this magnitude and duration would be extremely unlikely, requiring frequent injections of a significant amount of fluid repeated throughout pregnancy, not just occasional needle sticks. A single accidental exposure, even to a high concentration of this compound or direct needle stick, would be unlikely to result in the fetal harm described above. NIOSH has determined that the likelihood of these occurrences is minimal in a healthcare setting. Because oligohydramnios and the other resulting adverse developmental effects resolve in patients if treatment is stopped, a single accidental needlestick, even one at the human therapeutic dose, is not likely to cause adverse developmental effects. NIOSH criteria in *Procedures for the Developing the NIOSH List* state that adverse effects below the maximum human recommended dose generally support inclusion on the NIOSH *List*, but in the case of a single needlestick percutaneous exposure even a maximum human recommended dose is unlikely to result in fetal harm.

Oral exposure Bioavailability

No specific data on the bioavailability of pertuzumab via oral exposure was identified. Because of presystemic degradation in the gastrointestinal tract and poor absorption through the gastrointestinal epithelium due to their large size and polarity, bioavailability of monoclonal antibodies such as pertuzumab is very low [Wang et al. 2008; Keizer et al. 2010]. It would likely be significantly less systemically bioavailable when compared to the worst-case scenario proposed in the inhalation discussion above. Therefore, oral exposure is unlikely to pose a hazard to workers. NIOSH criteria in the *Procedures for the Developing the NIOSH List* state that adverse effects below the maximum human recommended dose generally support inclusion on the NIOSH *List.* Oral exposure to

a maximum human recommended dose would not result in systemic exposure that is high enough to cause a developmental effect.

Dermal exposure Bioavailability

No specific data on the bioavailability of pertuzumab via dermal exposure was identified. Similarly, dermal exposure is not expected to lead to relevant systemic exposure levels. Generally, molecules larger than 500 daltons are not easily or rapidly absorbed through intact skin [Bos and Meinardi 2000; Kimura et al. 2012]. It would likely be significantly less systemically bioavailable when compared to the worst-case scenario described in the inhalation discussion above. Therefore, pertuzumab is unlikely to pose a hazard to workers with noncontinuous exposure to pertuzumab on intact skin. Exposure to both intact or non-intact skin which is not continuous, due to the previously discussed very low bioavailability of such a large molecule to through the skin, is not expected to deliver a dose that would prove hazardous to workers. NIOSH criteria in the *Procedures for the Developing the NIOSH List* state that adverse effects below the maximum human recommended dose generally support inclusion on the NIOSH *List*. Skin exposure to a maximum human recommended dose would result in systemic exposure that is not high enough to cause a developmental effect.

Discussion

Evaluation of the hazard posed by pertuzumab shows that with repeated systemic exposures there is the potential to develop oligohydramnios as a result of delayed renal development in the fetus. The oligohydramnios can lead to other adverse developmental effects, including fetal death. This oligohydramnios is a result of the level of exposure of the fetus to pertuzumab and not a maternal effect. There was no NOAEL for developmental effects in the available animal developmental study and the lowest dose tested was 24% of the human expected dose by AUC. The toxicity of pertuzumab shows it is a clear developmental hazard. In the relevant early stage of pregnancy the fetal exposure may have even been lower, as fetal exposure levels were only measured at the end of the pregnancy when mechanisms of placental transfer would have increased the fetal exposure to pertuzumab. Evaluation of the hazard posed by pertuzumab shows that repeated systemic exposures at either of NIOSH's thresholds, a human dose or 10 mg/day, there is the potential to develop oligohydramnios and adverse developmental effects including fetal death. This meets the definition of a hazardous drug for addition onto NIOSH's 2016 List of Antineoplastic and Other Hazardous Drugs, in this case as a drug that poses a developmental hazard.

However, characterization of the hazard also indicates that in health care workplaces the relevant exposure routes are unlikely to lead to exposure levels frequently enough throughout the relevant periods of pregnancy that would cause adverse developmental effects. As a large monoclonal antibody (mAb) dermal, oral, and inhalation, routes of exposure have very limited bioavailability. Cases of oligohydramnios caused by treatment of pregnant patients with the similar HER2 targeting mAb trastuzumab have been reversible following the cessation of treatment with generally good outcomes for the fetus. This means that the relevant workplace scenario would require a repeated exposure at a level high enough to maintain oligohydramnios. With the limited dermal, oral, or inhalation bioavailability and the unlikelihood of repeated accidental injection exposures at a high enough volume required to result in sustained oligohydramnios, pertuzumab is not expected to pose a hazard to workers in healthcare workplaces. Therefore, despite posing a developmental hazard at low systemic doses, NIOSH is removing pertuzumab from the NIOSH *List*.

Table 1. Developmental effects that occur at the lowest tested dose.

Dose (Initial/every 3 weeks)	Multiple of human dose (AUC — FDA)	Effect	Incidence/Degree if available
30/10	0.242	Increase brain weight	12%
		Decreased kidney weight	62%
		Fetal death	2 of 12
		Embryonic death	1 of 12
		Abortion	1 of 12
		Embryo-fetal lethality total	4 of 12
		Oligohydramnios and discolored amniotic fluid	2 of 8
100/33.3	0.763	Increase brain weight	18%
		Decreased kidney weight	87%
		Fetal Death	1 of 12
		Embryonic death	3 of 12
		Abortion	2 of 12
		Embryofetal lethality total	6 of 12
		Oligohydramnios and discolored amniotic fluid	6 of 6
100/100	2.02	Increase brain weight	24%
		Decreased kidney weight	89%
		Fetal death	3 of 12
		Embryonic death	3 of 12
		Abortion	4 of 12
		Embryo-fetal lethality total	10 of 12
		Oligohydramnios and discolored amniotic fluid	2 of 2

FDA, 2012

External Review of the NIOSH Initial Recommendation

In January 2024, NIOSH published a notice in the Federal Register (89 FR 2614) seeking public comment on the initial NIOSH recommendation to remove pertuzumab from the *List*. Three public commenter provided feedback on the NIOSH recommendation for pertuzumab. NIOSH also conducted peer review of the draft pertuzumab

reevaluation. NIOSH received three peer reviews of the proposal to remove pertuzumab from the *List.* Following review and consideration of these comments, NIOSH has decided to remove pertuzumab from the *List*. The NIOSH responses to the peer reviewer and public comments are published in the Federal Register notice, *Hazardous Drugs: NIOSH List of Hazardous Drugs in Healthcare Setting, 2024* [NIOSH 2024].

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