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Assessment of Absent Subclavian Artery as Reported in a Rabbit Developmental Toxicology Study of Metaflumizone

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Introduction

In a rabbit developmental toxicity study of metaflumizone (BAS 320 I), a finding of absent subclavian artery was reported in several fetuses. The purpose of this analysis is to provide an expert opinion on the severity of this finding for affected offspring and its possible relation to treatment. In order to conduct this analysis, the client provided the unpublished report for the study in which this finding was observed:

- Schneider S, J Hellwig, B van Ravenzwaay. 2004a. BAS 320 I – Prenatal Developmental Toxicity Study in Himalayan Rabbits. Oral Administration (Gavage). BASF Project No. 40R0071/01116. BASF Aktiengesellschaft, 67056 Ludwigshafen, Germany. February 24, 2004; BASF DocID 2004/1009121.

The client also provided the following additional study reports and documents, which were used in our analyses:

- European Food Safety Authority (EFSA). 2013. Conclusion on Pesticide Peer Review: Conclusion on the peer review of the pesticide risk assessment of the active substance metaflumizone. EFSA Journal 11:3373.
- Schneider S, J Hellwig, B van Ravenzwaay. 2004b. BAS 320 I – Prenatal Developmental Toxicity Study in Wistar Rats. Oral Administration (Gavage). BASF Project No. 30R0071/01121. BASF Aktiengesellschaft, 67056 Ludwigshafen, Germany. February 24, 2004; BASF DocID 2004/1009122
- Schneider S, J Hellwig, B van Ravenzwaay. 2005. Statement. Refers the following report: BAS 320 I – Prenatal Developmental Toxicity Study in Himalayan Rabbits. Oral Administration (Gavage). BASF Project No. 40R0071/01116. Study completed on 24th February 2004; BASF Aktiengesellschaft, 67056 Ludwigshafen, Germany; BASF DocID 2005/1029364
- UK Competent Authority. 2016. CLP Report. Proposal for Harmonised Classification and Labelling. Substance Name: Metaflumizone. Version 1. March 2016.

For the purposes of developing an expert opinion on this matter, Exponent scientists relied on these reports, information available in the peer-reviewed literature, and personal expertise in developmental anatomy. The comparative anatomy and embryology of the great vessels that branch from the aortic arch are first described. Then, the findings from the rabbit study of metaflumizone are reviewed in detail to draw conclusions regarding the severity of this finding and its possible relation to treatment.

Comparative Anatomy of the Great Vessels Branching from the Aortic Arch

Aortic arch branching patterns have been shown to vary in both humans and rabbits. In humans, variations are particularly common in muscle attachments and vessel patterns (Moore and Dalley, 2006). The number, order and dimensions of the great vessels that branch from the arch of the aorta vary from the "normal" pattern in 12 – 26% of people across all ethnicities (e.g., Agur and Dalley, 2005; Jakani and Adair, 2010; Müller et al., 2011; Vučurević et al., 2013; Karacan et al., 2013; Lale et al., 2014; Kondori et al., 2016). Typically, these variations have little to no adverse health consequences and they are discovered as incidental findings during angiography or computerized tomography scans for unrelated indications. Similar incidences have been described in studies of cadavers of adults and spontaneously aborted fetuses (Patil et al., 2002; St. Gielecki et al., 2004; Patil et al., 2012; Budhiraja et al., 2013). Variations involving the subclavian arteries have been described as the most common intrathoracic major arterial anomalies (Freed and Low, 1997), with aberrant origins of this vessel reported in 2% - 16% of cases (Patil et al., 2002; St. Gielecki et al., 2004; Patil et al., 2012; Budhiraja et al., 2013). The right subclavian artery in humans has been found to originate variously as the fourth branch of the aortic arch (e.g., Kondori et al., 2016), as a direct branch from the descending thoracic aorta (St. Gielecki et al., 2004), or from the cervical region as a branch of the common carotid (Kutsche and Van Mierop., 1984).

The branching pattern of the great vessels from the aortic arch of the rabbit is also highly variable. Stump et al. (2012) found variations in the great vessels to occur in approximately 7% of 12,000+ rabbit fetuses at rates that ranged from 0% - 13.5% per litter and these often involved the subclavian arteries. The lability of this anatomical region in rabbits, with no obvious adverse health consequences, has been recognized for many years. Sawin and Edmonds (1949) described 20 variations in the branching patterns of the aortic arch great vessels in rabbits. Twenty-five years later, Angell-James (1974) similarly detailed 22 anatomical patterning variations of the great vessels. More recently, Ding et al. (2006) reported aberrant subclavian arteries in 2% of a small population of New Zealand white rabbits. Interestingly, Sawin and Edmonds (1949) noted that several races (now termed strains) of rabbits tended to be predisposed to exhibit a subset of the variant patterns. To investigate the potential hereditary or "familial" influences on the branching patterns, they bred rabbits of different populations together and performed multiple backcrosses. They concluded that variation in both the brachiocephalic and subclavian arteries were influenced by a "hereditary background" that predisposed offspring to exhibit the arterial branching patterns observed at necropsy. Further, the health of the rabbits did not appear to be affected by the branching patterns.

With respect to arterial patterns in the viscera, anatomical dissectors frequently make the statement that "*arteries are named by their region of distribution, not by their origin or*

branching pattern" (sic) (Tank, 2005). Thus, whether an anomaly in the patterning of the great vessels should be considered a malformation (i.e., a change that is irreversible and incompatible with or severely detrimental to the health and/or survival of the animal) or a variation should be based, not on from where the vessels originates, but rather, on whether it appropriately feeds into its region of distribution. In the case of the subclavian artery, the territory of distribution would be the upper limb.

Embryology of the Aortic Arch and Great Vessels

To understand the likely manner in which the subclavian artery findings reported in the rabbit teratology study of metaflumizone developed, it is necessary to review the embryology of the aortic arch and great vessels and how the aortic arch and great vessels of the embryo develop in concert with the heart. The embryology of this system is covered in detail in textbooks and chapters (e.g., Hamilton and Mossman, 1972; Harvey and Rosenthal, 1999; DeSesso and Venkat, 2010; Carlson, 2014; Schoenwolf et al., 2015) and will be briefly reviewed here. Once the embryo has undergone cephalocaudal folding, the heart attains its position in the ventral region of the chest. Outflow from the heart is connected to the dorsal aorta (the major artery of the body located adjacent to the vertebral column) by a series of paired arteries (aortic arches that run between the aortic sac (located ventral to the gut tube) and the dorsal aorta (located dorsal to the gut tube). In the region above and adjacent to the heart, the dorsal aorta is represented by bilateral vessels that merge into a single aorta below the level of the heart.

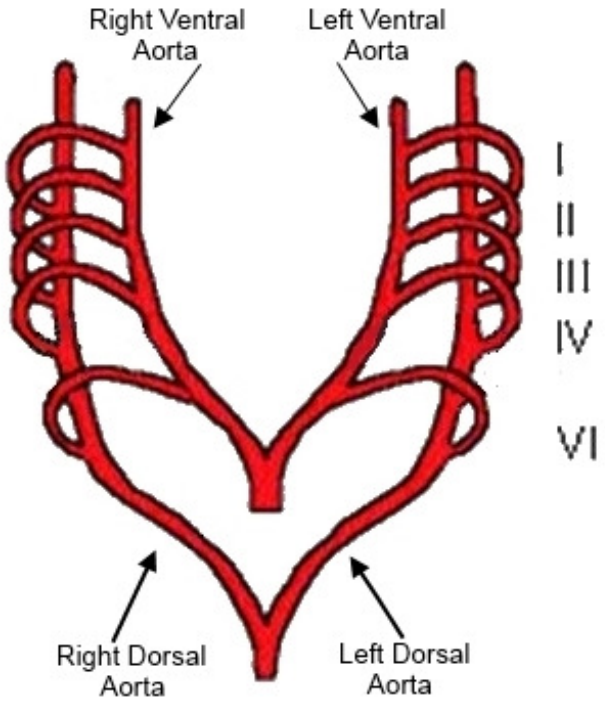

Figure 1. Diagram of the generalized plan of the aortae and aortic arches in mammals. The aortic arches are identified by Roman numerals. Note that aortic arch V is not depicted. The aortic arches appear in sequence and are not all present simultaneously. In order to achieve the adult configuration, portions of the aortae and aortic arches will degenerate during the course of embryological development.

There are five definitive pairs of aortic arches in mammals, numbered I, II, III, IV, and VI (aortic arch V is very transient or does not appear; Figure 1). The aortic arches develop in a

cephalocaudal direction such that aortic arch I develops first, followed by aortic arch II, etc. However, as aortic arch III appears, aortic arch I begins to disappear as an entity. By the time aortic arch IV is developing, aortic arch I is no longer present. The changes in the vasculature are partly driven by development of the neck, which appears as the embryonic face lifts off the chest and the head assumes an erect position. As development of the neck occurs, the face adjusts so that it looks forward rather than at the chest wall. To accomplish this, the right dorsal aorta between aortic arches III and IV (which tethers the head) atrophies, thereby releasing the head (Figure 2). There remains a single (bilateral) pair of arterial channels supplying the head, resulting in a configuration such that aortic arches I – III (or their derivatives) supply the head and neck and are separated from the lower aortic arches that remain in the chest.

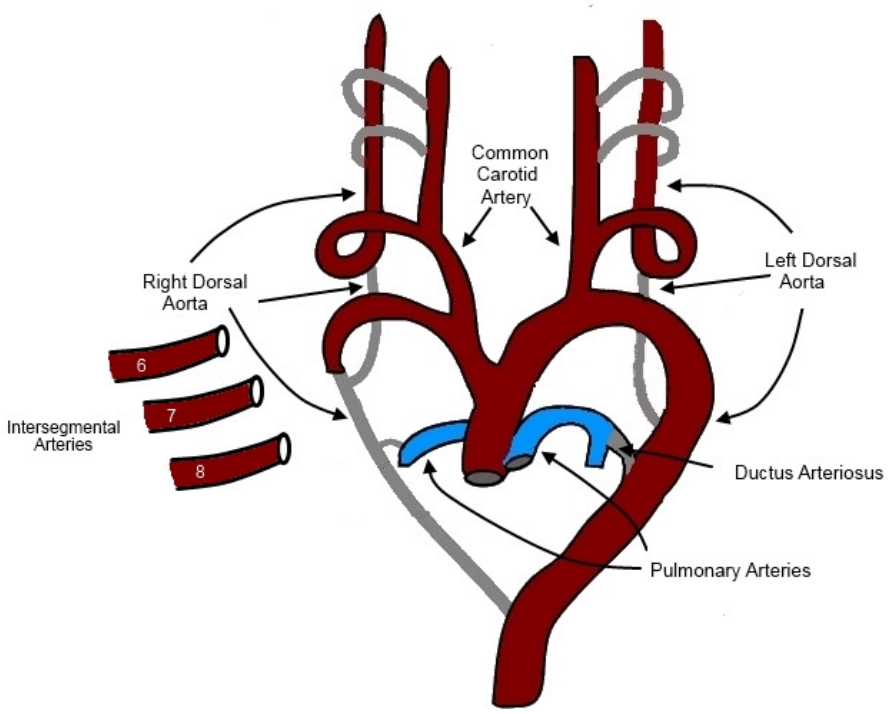

Figure 2. Diagram of the typical pattern of the aorta and great vessels. Structures that are colored gray are those that degenerated during development. Note in particular that the dorsal aortae between aortic arches III and IV degenerated on both sides allowing blood to access facial and neck structures by a single pair of major vessels (common carotids). Note also that the distal portion of the right dorsal aorta degenerates allowing blood to access the 7th intersegmental artery by means of the right aortic arch IV and a small portion of the proximal right dorsal aorta (this will give rise to the right subclavian artery). The proximal portions of aortic arches VI (shown in blue) give rise to the pulmonary arteries while the distal portions of degenerate.

The aortic arches contribute greatly to the vasculature of the upper chest, neck, and head. While all of the aortic arches are important, the two most caudal arches (aortic arches IV and VI) play integral roles in the development of the heart (Figure 2). Aortic arch IV is the vascular trunk that delivers blood to the body. On the left side, it develops into the arch of the aorta, which develops a branch that contributes to the left subclavian artery; on the right side, aortic arch IV, becomes

the stem of the right subclavian artery, which joins to the 7th cervical intersegmental artery that runs between the somites and vascularizes the developing limb bud (described in greater detail in DeSesso, 2017).

Embryology of Blood Supply to Limbs in Cases of Absent Subclavian Artery

The likely embryology that explains both the absence of the subclavian artery and a retained source of blood supply to the upper limb is depicted in Figure 3. The loss of the normally positioned subclavian artery occurs when the proximal portion of the right aortic arch IV, which normally joins with the 7th intersegmental artery to vascularize the limb bud, involutes along with the dorsal aorta between aortic arches III and IV. This results in the absence of the right subclavian artery as a branch of the aortic arch. In such instances, however, the distal portion of the right dorsal aorta does not involute. What happens in these cases is that the distal portion of the right dorsal aorta joins to the 7th intersegmental artery. Blood gets to the limb bud (and the arm in the fully formed individual) by traveling down the aorta to the point where the right dorsal aorta joins the definitive aorta. The blood then travels up the distal segment of the right dorsal aorta to the 7th intersegmental artery to gain access to the limb bud. In the adult condition, this artery would emerge from the aorta and travel along the vertebral column to approximately the level of the second or third rib and then would travel laterally to gain access to the arm via the 7th intersegmental artery to form the axillary artery (which is the continuation of the normal subclavian artery).

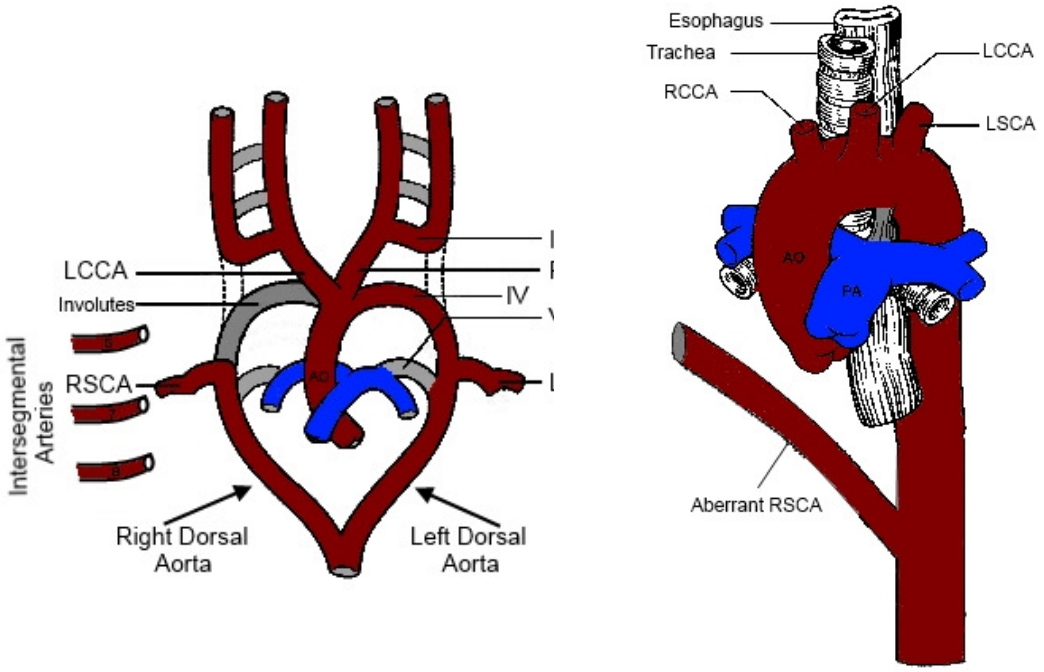

Figure 3. Aberrant right subclavian artery. The left panel illustrates the alteration in ontogenesis of the aortic system that can produce aberrant right subclavian artery. The proximal portion of the right dorsal aorta and all of aortic arch IV degenerate (gray sections on left of diagram) while the distal portion of the right dorsal aorta (which normally involutes) remains intact with its connection to the descending aorta (compare to Figure 2). The resulting adult configuration is depicted in the right panel. Note that the aberrant right subclavian runs across the posterior wall of the thorax and would be hidden from view by the right lung. (AO = Aorta; PA = pulmonary trunk; LCCA = left common carotid artery; LSCA = left subclavian artery; RCCA = right common carotid artery; RSCA = right subclavian artery; Roman numerals refer to aortic arches)

Rabbit Teratology Study of Metaflumizone (Schneider et al., 2004a)

In a developmental toxicity study of metaflumizone (BS 320 I; purity 96.9%), groups of pregnant Himalayan rabbits (n=25/group) were administered the test article from gestational day (GD) 6 to GD 28 at doses of 0, 30, 100, or 300 mg/kg/day. The dosing vehicle was 0.5% (w/v) aqueous methylcellulose (10 mL/kg). The study investigators reported treatment-related maternal toxicity at the high dose of 300 mg/kg/day, including clinical signs (i.e., lateral position, ataxia, poor general state, blood in bedding, and/or no defecation in the last treatment days) in 4 high dose rabbits, as well as abortion in 2 of these does and moribund condition in another. However, no effects of treatment were observed on mean maternal body weight or body weight gain. Further, litter parameters (i.e., rates of pre- and post-implantation losses, the number of resorptions, the number of live fetuses, and fetal sex ratio) were unaffected by treatment. Fetal body weights, however, were slightly reduced (approximately 7%) at this dose and this decrease was attributed to an increased percentage of runts (i.e., fetuses with body weights at least 25% less than the concurrent control mean value). Additionally, an increase in the incidence of incomplete ossification of the sternebra (a variation) was reported at 300 mg/kg/day; however, an increase in other external, visceral or skeletal anomalies was not seen. The possible exception to this conclusion is a finding of absent subclavian artery reported in 1, 1 and 3 fetuses from the 30, 100, and 300 mg/kg/day dose groups, respectively (Table 1). However, the incidence of this finding at all doses was considered to be similar to that observed in the historical control data for Himalayan rabbits, and thus, unrelated to treatment (Schneider et al., 2005). Further, no indications of maternal or fetal toxicity were observed at doses of 30 and 100 mg/kg/day. Based on these data, the study investigators concluded that the no observed adverse effect level (NOAEL) for both maternal and prenatal developmental toxicity was 100 mg/kg/day.

Table 1. Fetuses reported with absent subclavian artery in the rabbit developmental toxicity study of BAS 320 I (metaflumizone).

Dose (mg/kg/day)	Doe/Litter	Fetus	Other Anomalies
30	35	2F	Absent gallbladder, absent lung lobe, supernumerary rib
100	74	3M	Absent gallbladder, right-sided aortic arch, absent lung lobe, heart ventricular septal defect, fused sternebrae, incomplete ossification of the hyoid, supernumerary rib, unossified talus, splitting of skull bone
300	85	1M	Unossified sternebra, misshapen sternebra, incomplete ossification of the hyoid
	90	2M	Incomplete ossification of the sternebra
	94	1D	Paw hyperflexion, absent lung lobe, incomplete ossification of the sternebra, supernumerary rib

F = female; M = male; D = dead

Despite the conclusion of the study investigators, the European Food Safety Authority (EFSA), in its examination of the study data, concluded that the increased incidence of absent subclavian artery should lead to classification of metaflumizone as Repr. 2 H361d (suspected of damaging the unborn child) (EFSA, 2013). The basis upon which this proposal was made, however, was not expounded upon. In its proposal for the classification for metaflumizone, the UK Competent Authority agreed with EFSA's recommendation of Repr. 2 H361d (UK Competent Authority, 2016), noting that the fetal incidence of absent subclavian artery at the high dose in the study (3/131 fetuses; 2.3%), was slightly outside of the maximum fetal incidence reported in the historical control data (3/146 fetuses; 2.1%).

Expert Assessment and Opinion

In evaluating the data on absent subclavian artery available from the rabbit teratology study of metaflumizone, a few pertinent issues must be considered. First, the affected fetus noted at the mid-dose (100 mg/kg/day) presented with additional and related anomalies, including a right-sided aortic arch and a ventricular septal defect of the heart. These anomalies are correlated with disruption of the hemodynamics in the developing heart and, thus, should be considered "syndromic" in contrast with an isolated defect as recorded for the other instances of aberrant subclavian artery. When a spectrum of observations (a syndrome) occurs in a given organ system, it suggests that the mechanism is less targeted and is not the same as is present in isolated events (Stump et al., 2012) and is typically not treatment-related. Second, right-sided aortic arch is a laterality (or situs) defect (Shapiro et al., 2014) which have not been reported to be treatment -related. Third, when a right-sided aortic arch appears in humans, it is often found in conjunction with an aberrant subclavian artery (Białowąs et al., 2000), suggesting a link between the two findings. Taken together, this information indicates that this finding likely not treatment-related.

Second, with regard to the findings at the high dose (300 mg/kg/day), one of the affected fetuses was reported as dead. In prenatal developmental toxicity studies, anomalies are typically only assessed in live fetuses. As noted in Tyl and Marr (2012),

> "The uterine contents (i.e., number of total implantation sites, resorptions, dead fetuses and live fetuses) should be recorded (see below). Dead fetuses should be weighed, examined externally and saved in neutral buffered 10% formalin…Each live fetus is given a fetal number to track subsequent information." (pp. 163-4)

The subsequent information that may be tracked in live fetuses includes visceral and skeletal anomalies. Dead fetuses, on the other hand, are not numbered for further examination. Thus, fetuses that are designated as "dead" are not meant be included in the tabulation of structural anomalies. The tracking of structural anomalies in live fetuses only is further shown in the equation presented by Stump et al. (2012) for the presentation of fetal morphological findings:

$$Viable\ fetuses \frac{affected}{litter} (\%) = \frac{No.of\ viable\ fetuses\ affected\ per\ litter}{No.of\ viable\ fetuses\ per\ litter} \times 100$$

Based on this information, the dead fetus with the absent subclavian artery should not have been included in the tabulation of structural anomalies. Therefore, the actual fetal incidence of absent subclavian artery at the high dose of 300 mg/kg/day is 2/131 fetuses, or 1.5%, which is within the historical control range.

Finally, it is our opinion that the finding of "absent subclavian artery" should be considered a variation rather than a malformation for the following reasons.

1. The branching pattern of the great vessels, including the subclavian arteries, is variable in humans and especially so in rabbits (as discussed above).
2. The subclavian artery is the supply of blood to the limbs and there were no malformations of the upper extremities reported in the affected fetuses. This means that the limbs received adequate blood supply.
3. The protocol for visceral examinations followed by the laboratory involved examining the branching pattern of the great vessels from the arch of the aorta and deeper dissection into the chest to identify the source of blood supply to the limbs was not performed (S. Schneider, 2015; BASF DocID 2015/1134422). This means that, although it must have been present, the alternate route of blood supply to the limbs was not determined.
4. The embryology associated with the patterning of the great vessels from the arch of the aorta or aorta proper and the major variations of that patterning are well known and account for the probable route of blood supply to the upper extremities (as discussed above).
5. In circumstances when the territory of distribution for the subclavian artery (i.e., the upper limb) is not malformed, and given the complex embryology of that vessel (as discussed below), then the finding should be considered an anatomical variation rather than a malformation

Conclusions

Based on the above information, it is our expert opinion that:

Regarding the finding of absent subclavian artery

- Findings of absent subclavian artery in isolation are different from a syndromic collection of anomalies of the heart and great vessels (including absent subclavian artery) reported in a single fetus at 100 mg/kg/day.
- Morphological findings in dead fetuses are useful for trying to determine a cause for the demise of a fetus, but should *not* be tabulated with observations in living fetuses.
- The incidence of absent subclavian artery in living fetuses of the high dose group of the rabbit developmental toxicity study is 2/130 (1.5%) and *is within the range of the laboratory's historical control data* for fetal incidence(3/146 or 2.1%). This is also consistent with reported incidence of aberrant subclavian arteries in New Zealand white rabbits of 2% (Ding et al., 2006).
- Variation in the subclavian artery in rabbits is subject to hereditary influence and is without apparent adverse health consequence (Sawin and Edmonds, 1949).

Regarding the terminology used to describe the finding of absent subclavian artery

- Arterial branching patterns vary considerably between individuals. This is true for humans as well as rabbits.
- The vascular pattern for branching of the great vessels from the aortic arch is especially labile in rabbits.
- The finding of absent subclavian artery in the rabbit developmental toxicity study was based only on visual examination of the aortic arch without further dissection to ascertain how the upper limb was vascularized.
- The upper limbs of the subject rabbit fetuses were not malformed or atrophied, indicating that they must have received appropriate blood supply during development.
- The known embryology of "aberrant" subclavian artery involves an alteration in the normal degeneration pattern of the aortic arch system resulting in origination of the subclavian artery from the descending thoracic aorta.

- The best description of this type of observation is “anatomical variation” as it is described in the human literature.

Thus, the incidence of absent subclavian artery in this study are within those in the historical control data, making it both unlikely that they are treatment-related and of insufficient severity to warrant their use as the basis to classify metaflumizone as a reproductive hazard.

Limitations

The expert opinion expressed herein is made to a reasonable degree of scientific certainty. Exponent scientists reserve the right to supplement this report and to expand or modify the conclusions and findings based on review of additional, credible materials should they become available through additional work. This assessment may not adequately address the needs of other users of this report, and any re-use of this report or its findings and conclusions as presented herein are at the sole risk of the user.

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