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Is omphalocele a non-specific malformation in New Zealand White rabbits?

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ABSTRACT

We evaluated the incidence of omphalocele, a malformation that occurs sporadically in many studies. We assembled data on external malformations using all treatment groups from every study published in three major journals over the past 35 years using New Zealand White rabbits. Fifty-eight papers were included: 4905 litters and 36,977 fetuses. Omphalocele was reported in 43% and was among the most common defects, occurring at a rate of 1.10% (litter) and 0.16% (fetus). The defect did not appear to be treatment-related, although it may have been in two studies, based on rate and dose-responsiveness. Removing these two studies from the analysis, the defect was still prevalent (0.77% litter, 0.11% fetal incidence). Three studies evaluated the effects of food restriction and omphalocele was observed with food restriction in two of them, suggesting that decreased maternal weight gain or food consumption may be causal. Otherwise, it appears to be spontaneous and common.

1. Introduction

The overall malformation rate in rabbit developmental toxicity studies is in the range of 1–2% [1], although some investigators have cited rates of less than 1% [2]. In a typical study using twenty or so pregnant rabbits per group, there are likely to be only a few fetuses with malformations, and the incidence of each specific malformation even lower. It is not uncommon in the conduct of developmental toxicity studies to observe one or two instances of a malformation in a single group. If these occur in the control then it is obvious that they are attributable to spontaneous background, but if they occur in a treatment group the interpretation is more difficult. Therefore, it is customary to rely on historical control data sets to aid in the interpretation.

Contract laboratories and large industry labs compile their own historical control data. However, even very active labs are limited in the number of studies they can draw from to compile these data. For example, Spence [3] presented three years of rabbit historical control data from Merck's research laboratories, consisting of 350 New Zealand White litters and 236 Dutch Belted litters. Posobiec et al. [4] shared the historical control data from Covance and Charles River Laboratories for 2014, which consisted of 993 New Zealand White litters and 180 Dutch Belted litters. While these data are useful, they still represent a small sample size for reliably estimating the incidence of relatively rare events. Recognizing this limitation, the Middle Atlantic Reproduction and Teratology Association (MARTA) compiled a large data set from a survey of 21 member organizations for the period of 1989–92. This database consisted of 2794 New Zealand White rabbit litters and 20,071 fetuses [5], large enough to provide reasonable estimates for the rates of many individual malformations.

Another approach for compiling information on malformation incidence is to include data from all groups in a study. While this is obviously not equivalent to a historical control database, it does increase by a factor of four the amount of data available. Presence or absence of dose-responsiveness can then be used to provide an indication as to whether any particular effect was treatment-related or was less specific. Whether that lack of specificity was attributable to the stress of treatment or was spontaneous background would not be discernible through this process.

We were particularly interested in determining the rate of omphalocele or umbilical hernia in New Zealand White rabbit fetuses, and whether it was a non-specific malformation, after noting its occurrence sporadically in many studies, including in the presence of maternal toxicity. Omphalocele was the most common external malformation in New Zealand White rabbits in the MARTA database [5]. Umbilical hernia was reported separately in that database, and when combined with omphalocele the incidence

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Table 1
Summary of studies meeting the inclusion criteria.

Reference	Chemical	Dose levels	Litters/ fetuses in each dose level	Omphalocele Litter, fetal incidence	Other external malformations	Maternal toxicity
[7]	Tetrachloroacetone	0, 1, 5, 10 mkd	0: 21/158 1: 19/132 5: 15/112 10: 18/134	1/15, 1/112 in mid dose	Mid dose: gastroschisis, bent tail, exencephaly (1 instance of each); rotated limb, I each in low, mid and high dose; spina bifida, 1 instance in high dose	One death at 10 mkd
[8]	Epichlorohydrin	Epi: 0, 2.5, 25 ppm inhalation	Epi 0: 23/156 2.5: 18/127 25: 16/106		AC: short tail (2 fetuses in one litter, low dose); rotated paw, 1 instance, high dose; anophthalmia, 1 instance low dose; hydrocephalus, 1 instance, control	A maternal death at high dose for each chemical
	Allyl chloride	AC: 0, 30, 300 ppm inhalation	AC 0:21/141 30: 17/127 300: 15/108			
[9]	Propylene glycol monomethyl ether	0, 500, 1500, 3000 ppm (inhalation)	0: 28/ 199 500: 29/198 1500: 27/194 3000: 24/173	1/24, 1/173 in high dose	Arthrogryposis: 1/28, 2/199 in control; 1/29, 2/198 in low dose, 2/27, 2/194 in mid dose; ablepharia, 1 instance in control; spina bifida, 1 instance in mid dose; craniorachischisis, 1 instance in mid dose	4/33 died at high dose, 90% decrement in weight gain during dosing period at mid dose, weight loss during dosing at high dose
[10]	triclopyr	0. 10, 25 mkd	0:12/97 10: 17/147 25: 12/108		Low dose, one instance each of hydrocephaly, microphthalmia; high dose, one instance of rhinencephaly/ encephalocele/ proboscis	Significant weight gain decrement during dosing in both dose groups
[11]	3,6-dichloropicolinic acid	0, 110, 250 mkd	0:14/122 110: 11/88 250: 11/91	1/14, 1/122 in control	Anencephaly, 1 instance in low dose	none
[12]	Omadine MDS	Vehicle control, untreated control, 0.45, 1.5, 5 mkd	Vehicle: 11/64 Untreated: 16/88 0.45: 12/75 1.5: 12/77 5: 11/50		Vehicle control: anencephaly, carpal flexure, 1 instance each; untreated, 1 instance of gastroschisis; high dose: tail anomaly, hydrocephaly, 1 instance each	High dose, decreased weight gain during dosing period
[13]	o-dichlorobenzene	o-DCB: 0, 100, 200, 400 ppm by inhalation	o-DCB 0: 21/139 100: 22/126 200: 21/138 400: 24/169	2/28, 2/218 in high dose p-DCB	o-DCB: control: single instances of anal atresia, hypoplastic tail, rotated hindlimb, anencephaly, and 2 instances in 2 litters of forelimb flexure; low dose: 1 instance of cyclopia, hydrocephaly, 2 instances of rotated hind limb; high dose: 2 instances in 2 litters of forelimb flexure and rotated hind limb, single instance of anencephaly	Significant effect on maternal weight gain at all dose levels for o-DCB, and at mid and high doses for p-DCB
	p-dichlorobenzene	p-DCB: 0, 100, 300, 800 ppm by inhalation	p-DCB 0:28/210 100: 23/176 300: 22/175 800: 28/218		p-DCB: control: single instance of spina bifida; low dose: 2 instances in 1 litter of forelimb flexure; mid dose: 1 instance of forelimb flexure; high dose: 1 instance of acephaly, 4 instances in 2 litters of forelimb flexure.	
[14]	Diethylene glycol monobutyl ether	0, 100, 300, 1000 mkd applied topically	0: 19/143 100: 19/149 300: 18/125 1000: 16/115		Control: 1 instance each of short tail, limb flexure; high dose: 1 instance of acrania, 2 instances of limb flexure	Some skin irritation at mid and high doses