

## Further Development 14.8

### Retinoic acid and glyphosate as teratogens

Why is there a warning label on acne medicines telling the potential buyer not to use these medicines if they are pregnant? The answer is that retinoic acid, the active ingredient in many acne medicines, is a powerful teratogen. This may seem surprising, since retinoic acid is a compound that is manufactured by the body for normal development. However, even a compound involved in normal development can have deleterious effects if it is present in large enough amounts or at particular times. Retinoic acid (RA) is a vitamin A derivative that is important in specifying the anterior-posterior axis and in forming the jaws and heart of the mammalian embryo. As Piersma and colleagues (2017) have written, “The region-specific homeostasis of RA in the embryo is in many ways the driving force determining developmental cell proliferation versus differentiation. As a consequence, RA concentrations are carefully controlled in time and space in the developing embryo.”

In its pharmaceutical form, 13-*cis*-retinoic acid (also called isotretinoin and sold under the trademark Accutane) has been useful in treating severe cystic acne and has been available for this purpose since 1982. The deleterious effects of administering large amounts of RA (or its vitamin A precursor) to pregnant animals had been known since the 1950s (Cohlan 1953; Giroud and Martinet 1959; Kochhar et al. 1984). However, about 160,000 women of childbearing age (15–45 years) have taken isotretinoin since it was introduced, and some have used it during pregnancy. Isotretinoin-containing drugs now carry a strong warning against their use by pregnant women. In the United States, retinoic acid exposure is a critical public health concern because there is significant overlap between the population using acne medicine and the population of women of childbearing age—and because an estimated 50% of pregnancies in the U.S. are unplanned (Finer and Zolna 2011).

Lammer and co-workers (1985) studied a group of women who inadvertently exposed themselves to RA and who elected to remain pregnant. Of their 59 fetuses, 26 were born without any noticeable anomalies, 12 aborted spontaneously, and 21 were born with obvious anomalies. The affected infants had a characteristic pattern of anomalies, including absent or defective ears, absent or small jaws, cleft palate, aortic arch abnormalities, thymus deficiencies, and abnormalities of the central nervous system. These anomalies are largely due to the failure of cranial neural crest cells to migrate into the pharyngeal arches of the face to form the jaw and ears (Moroni et al. 1994;

Studer et al. 1994). Radioactively labeled RA binds to the cranial neural crest cells and arrests both their proliferation and their migration (Johnston et al. 1985; Goulding and Pratt 1986). The teratogenic period during which cranial neural crest cells are affected occurs on days 20–35 in humans (days 8–10 in mice).

Retinoic acid probably disrupts these cells in several ways. One mechanism is that excess RA activates the negative feedback pathway that usually ensures the proper amount of this compound. Transient large increases in RA thus activate the synthesis of RA-degrading enzymes, causing a long-lasting *decrease* of RA. It is this deficiency in RA that results in the malformations (Lee et al. 2012). This explains why high amounts of retinoic acid produce phenotypes similar to those seen in deficiencies of retinoic acid.

### **Glyphosate**

Interference with RA signaling may be a wider public health concern for another reason. Glyphosate-based herbicides (such as Roundup®) have been reported to upregulate the activity of endogenous RA (Paganelli et al. 2010). When *Xenopus* embryos were incubated in solutions containing ecologically relevant concentrations of these herbicides, RA-responsive reporter gene activation was dramatically altered, and the embryos exhibited cranial neural crest defects and facial features similar to those seen in RA teratogenesis (**FIGURE 1**).

Epidemiological evidence on humans as well as laboratory experiments on rodents (Pu et al 2020) suggest that glyphosate exposure in utero may cause autism-like behavioral abnormalities, and that glyphosate exposure as adults increases the risk of cancers, especially certain lymphomas (Weisenburger 2021).

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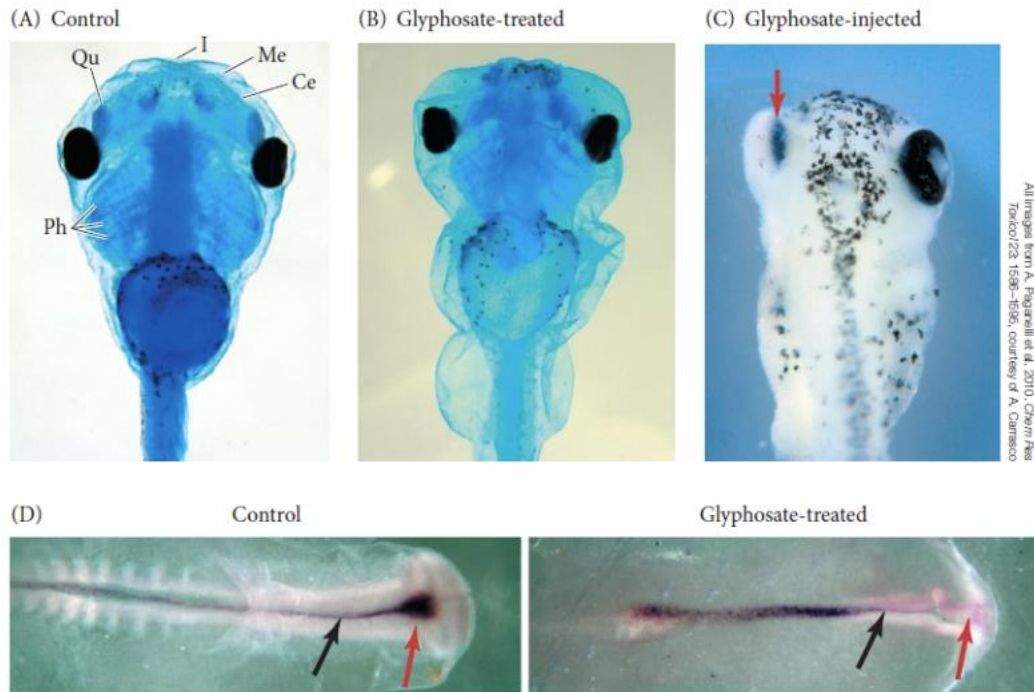
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**{References are in Chapter 23 file}**

**FIGURE 1**



All images from A. Paganelli et al. 2010. *Chem Res Toxicol* 23: 1586–1595, courtesy of A. Carrasco

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Glyphosate herbicide teratogenicity. (A) *Xenopus* tadpole raised under control conditions, stained with alcian blue to show facial cartilages. Ph, pharyngeal; Ce, ceratohyal; I, infrarostral; Me, meckel; Qu, quadrate. (B) *Xenopus* tadpole raised in environmentally relevant concentrations of glyphosate and similarly stained. Its pharyngeal arches and midline facial cartilage (cranial neural crest derivatives) failed to develop properly. (C) If an embryo is injected such that only one side (arrow) is exposed to glyphosate, that side shows cranial neural crest anomalies. (D) Control chick embryos show *sonic hedgehog* gene expression in the notochord (black arrow) and prechordal mesoderm (red arrow). Chick embryos grown in glyphosate show a severe reduction of *sonic hedgehog* expression in the prechordal (craniofacial) mesoderm.

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