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### **Cost-effective stereology in developmental toxicity**

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In a regulatory developmental neurotoxicity (DNT) study (EPA OPPTS 870.6300) with rats we used a tiered morphological approach (brain size→ microscopic slide reading→ 2D linear morphometry→ 3D stereology) to demonstrate that prenatal exposure to methylazoxy methanol (MAM; doses up to 7.5 mg/kg/day; PN 13-15) causes substantial effects on brain morphology, as shown by 2D and 3D morphometry/stereology. The effects went unrecognized during microscopic slide reading. Likewise, significant effects of perinatal exposure to methyl mercury (MeHg; doses up to 1 mg/kg/day; GD 6-PD10) were demonstrated, however, by 3D stereology only. Especially total cell numbers and brain region volume showed high discriminative power. So, it was concluded that stereology offers the best opportunity to detect early morphological changes in the developing brain and adverse effects of drugs, chemicals or food components thereon.

Counting cells is a time consuming job, but volume estimates can be determined fast as long as the investigated region can clearly be defined and borders demarcated. Hereto, we developed a 'novel' atlas of the rat brain defined in ten major regions. Together with multi-brain embedding/sectioning/sampling, the renewed and reversed tiered approach (brain size→ 3D stereology → 2D linear morphometry→ microscopic slide reading) proved to be sensitive and efficient. The estimates of brain region volumes appeared to be sensitive first-tier indicators to pinpoint the focus for toxicity and to narrow-down the workload. We could demonstrate that stereology is now within reach of cost-effective regulatory DNT testing.

*This project is financed by the American Chemistry Council (Contract no. 1847). The views given here are solely the responsibility of the authors.*