

# TOXICITY TESTING REQUIREMENTS, METHODS AND PROPOSED ALTERNATIVES

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## I. INTRODUCTION

Toxicology is the study of chemical substances that harm biological organisms.<sup>1</sup> Toxic exposure can occur transdermally through contact with the skin, orally and via inhalation.<sup>2</sup> Toxicity testing is necessary to provide some basis for the regulation of substances that humans and other living things may come into contact with, intentionally or not. It is used to determine the safety of cosmetics, pharmaceuticals, food additives, pesticides, chemicals, additives and consumer products. A toxic effect can result from a natural or a manufactured substance and manifest a variety of symptoms, both immediate and long-term.<sup>3</sup> As a result, toxicity testing introduces a variety of methods and rates of exposure to the test organism, in order to formulate a more accurate assessment of the risk of harm that the test substance may pose to human health and the environment.

Most human knowledge of the toxicity of various chemicals is the result of animal research, though it is intended for the most part to extrapolate predicted human physiological response.<sup>4</sup> Although there is no accurate numerical statistic available, animals are used by the millions annually for product testing in the United States. Under the Federal Animal Welfare Act, only dogs, cats, primates, rabbits, hamsters and guinea pigs are protected, and thus statistically counted for agency reporting to the U.S. Department of Agriculture.<sup>5</sup> Undoubtedly countless more rodents [often mice and rats which constitute 85-90% of laboratory animals used] and other animals are experimented on annually and their

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\* J.D. 2003 University of California, Davis School of Law. B.A., B.Phil & M.A. in Philosophy, National University of Ireland, Maynooth. A heartfelt thanks to the many pets that have touched and so greatly enhanced my life. This article is dedicated to those nonhumans who have perished in the name of science, those who continue to suffer, and those yet to be born, for the use of their bodies.

<sup>1</sup> Joanne Zurlo, Deborah Rudacille, and Alan M. Goldberg, *Animal and Alternatives in Testing: History, Science, and Ethics*, Johns Hopkins University Center for Alternatives to Animal Testing (2002), at [http://caat.jhsph.edu/pubs/animal\\_alts/animal\\_alts.htm](http://caat.jhsph.edu/pubs/animal_alts/animal_alts.htm).

<sup>2</sup> *Id.*

<sup>3</sup> *Id.*

<sup>4</sup> *Id.*

<sup>5</sup> Animal Welfare Act, 7 U.S.C.A. § 2131 (West 1999).

numbers unreported.<sup>6</sup> In 1985 the Office of Technology Assessment estimated that in the mid-1980s 17 to 22 million vertebrates were used annually for all research purposes combined.<sup>7</sup> The Humane Society of the United States estimates that of these, at least 55% are used for pharmaceutical and other product toxicity testing.<sup>8</sup> These millions suffer and die for the benefit of humans, yet anaesthesia has become common practice in the laboratory only in the last decade.<sup>9</sup> Plus, such suffering does not always benefit humans. Many animal tests have led to results that are inaccurate in humans, and some have led to death and deformity caused by products that initially appeared to be nontoxic to nonhumans. For these reasons the incorporation of new technologies in toxicity testing that better represent human tissue are currently under investigation and subject to the federal legislation that will be discussed below.

Regulatory agencies oversee an estimated minimum of 80,000 chemicals currently in use in the United States, as well as the introduction of over 2,000 new substances annually.<sup>10</sup> These numbers present regulatory challenges to the agencies charged with the promulgation of health and safety regulations for substances. This is because the testing guidelines must be thorough enough to assure a minimal risk to human and environmental health without over-burdening industry. This is especially difficult as toxic effects are often chronic in nature, and result from long-term exposure, the testing for which if completed over a period of several years, might render the product obsolete before it even enters the market place. Technology and market competition necessitate expediency of product approval. If extensive tests for every new chemical or product were conducted over a period of decades, the costs to the industry would be so prohibitive that the benefits of such technological developments would rarely if ever be reaped by the public. Chilling of industry and technology would become widespread and those whom toxicity testing guidelines seek to protect would undoubtedly be worse-off in the long-term through the deprivation of such advancements. These considerations beg the question as to the types of tests that should be required in order to assure accurate risk assessment of a substance. My analysis of this problem includes: the effectiveness of testing methods, reliability of test data, reasonableness of the burden on industry, regulatory approval and the ethical considerations pertaining to the above. It is no longer necessary to rely strictly on laboratory animal tests for biological re-

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<sup>6</sup> Humane Society of the United States (2002), at <http://www.hsus.org/ace/11396>.

<sup>7</sup> *Id.*

<sup>8</sup> *Id.*

<sup>9</sup> *Id.*

<sup>10</sup> *Congressional Office of Technology Assessment: Congress Screening and Testing Chemicals in Commerce*, OTA-BP-ENV-166, U.S. Washington: Office of Technology Assessment 126 (1995).

sponse data, and the adoption of alternative methods will bring benefits of accuracy, cost and time efficiency in addition to the reduction of animal suffering.

## II. FEDERAL TOXICITY TESTING REQUIREMENTS

Toxicity testing is required by federal law in a variety of contexts. There are four federal agencies which require animal tests: the Environmental Protection Agency (EPA), the Food and Drug Administration (FDA), the Consumer Product Safety Commission (CPSC) and the Occupational Safety and Health Administration (OSHA).

### A. EPA

The Environmental Protection Agency is required to conduct toxicity tests on laboratory animals in accordance with the Toxic Substances Control Act, air and pesticide programs.<sup>11</sup> For example, the EPA has implemented its High Production Volume Challenge Program (HPV program), wherein it plans to test 2,800 chemicals and will perform toxicity tests on over 100,000 animals.<sup>12</sup> One of the substances at issue is cyclohexanol, a chemical used in nylon, plastic, and paint manufacturing.<sup>13</sup> The proposed experiments will entail the confinement and exposure of 1,000 rats to high amounts of cyclohexanol fumes through forced inhalation.<sup>14</sup> These tests will be duplicative as the chemical has already undergone extensive tests and is known to cause reproductive disorders.<sup>15</sup> A coalition of organizations including Physicians Committee for the Responsible Practice of Medicine and People for the Ethical Treatment of Animals has filed notice of intent to sue with the EPA, charging that the planned tests violate a provision of the Toxic Substances Control Act which requires that public commenting sessions be held in accordance with rulemaking procedures.<sup>16</sup> As many of the tests are redundant and involve substantial animal cruelty at a great expense to taxpayers, these groups urge that the HPV program be reconsidered and the public afforded the opportunity to comment.

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<sup>11</sup> See Toxic Substances Control Act, 40 C.F.R. § 798.6560 (Lexis, 2002). See also

<sup>12</sup> *DuPont, Honeywell Accused of Unnecessary Animal Cruelty; Doctors, Animal Protectionists Charge Companies with Violating EPA Agreement*, U.S. Newswire, Washington, March 25, 2002, at <http://www.usnewswire.com/topnews/search4/0325-124.html>.

<sup>13</sup> *Id.*

<sup>14</sup> *Id.*

<sup>15</sup> *Id.*

<sup>16</sup> Press Release, Physicians Committee for Responsible Medicine, Doctors Initiate Legal Challenge to Testing Program, (Feb. 12, 2002) (where is it on file?) (press release).

### B. FDA

The Food and Drug Administration likewise requires animal tests of drugs currently used for human consumption and applications for FDA approval to market a new drug.<sup>17</sup> It also promulgated extensive toxicity guidelines for food ingredients in the agency authored "Redbook 2000".<sup>18</sup> FDA regulations prevent color additives that are carcinogenic and other food additives that are injurious to health from entry into interstate commerce.<sup>19</sup>

### C. CPSC

The Consumer Product Safety Commission requires experiments pursuant to the Poison Prevention Packaging Act of 1970<sup>20</sup> and the Federal Hazardous Substances Act.<sup>21</sup> It has authority to set safety standards for products that pose an unreasonable risk of injury or illness, and to recall those that pose a "substantial risk of injury to the consumer."<sup>22</sup>

### D. OSHA

The Occupational Safety and Health Administration also requires animal toxicity data for the promulgation of regulations pertaining to hazardous substances in the work place.<sup>23</sup> OSHA identifies carcinogens in the workplace and sets the standard for their regulation so that no worker suffers a "material impairment of health."<sup>24</sup>

The preceding agency legislation illustrates the prevalence of mandatory toxicity testing as a means of assessing the risk posed by the substance at issue to biological organisms. Where the risk is sufficiently low, the chemical will receive regulatory approval. This determination is commonly made through the analysis of animal experimentation data. Federal agencies use the following principles to identify potential hazards through risk assessment:

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<sup>17</sup> Food, Drug and Cosmetic Act, 40 C.F.R. § 79.61-3, (Lexis, 2002). (I am not clear about what CFR you are referring to here. §79.61 is about fuel additives. Are you referring to a certain section of the FDCA or a certain CFR?)

<sup>18</sup> *Redbook 2000*, Center for Food Safety and Applied Nutrition, (Oct. 2001), 21 C.F.R. §§ 312.23, 314.50 (2002). at at [http://www.cfsan.fda.gov/~red-toca.html](http://www.cfsan.fda.gov/~redbook/red-toca.html).

<sup>19</sup> American Council on Science and Health, *Of Mice and Mandates: Animal Experiments, Human Cancer Risk and Regulatory Policy*, (July 1997) at: <http://www.acsh.org/publications/booklets/mice.pdf>.

<sup>20</sup> Poison Prevention Packaging Act of 1970, 16 C.F.R. §1702.9 (2002).

<sup>21</sup> Federal Hazardous Substances Act, 16 C.F.R. §§ 1702.9, § 1500.135 (Lexis 2002).

<sup>22</sup> Federal Hazardous Substances Act, 16 C.F.R. § 1702.9 *Supra* note 20.

<sup>23</sup> Occupational Safety and Health Administration, 29 C.F.R. § 1910.1200 (Lexis 2002).

<sup>24</sup> *Id.* 29 CFR 1910.1200 (Lexis 2002)

- (1) hazard identification and the evaluation of the potential to produce adverse biological effects,
- (2) dose-response assessment and the determination of the influence of exposure levels on adverse effects,
- (3) exposure assessment and the estimation of anticipated exposure to an agent, and
- (4) risk characterization and the description of the nature and often the magnitude of the risk, including attendant uncertainty.<sup>25</sup>

These criteria aid in the determination of the toxicity of a chemical and thus affect its manner of regulation by a federal agency or program. The relevant data inherently include actual biological response to exposure as a factor for consideration, without which the process of risk assessment itself would be far less accurate. In this regard, nonhuman animals provide a biological proxy for the determination of human response to potentially toxic substances.

### III. TOXICITY TESTING ON ANIMALS

The Toxic Substances Control Act defines a “toxic effect” as “an adverse change in the structure or function of an experimental animal as a result of exposure to a chemical substance.”<sup>26</sup> Such changes may be effected via acute, subchronic or chronic exposure studies.<sup>27</sup> Acute toxicity tests measure the immediate effects of exposure with an estimated time for peak effect of approximately eight hours after the initial exposure.<sup>28</sup> Subchronic toxicity tests occur over a period of weeks, while chronic effects tests measuring long-term exposure last several months.<sup>29</sup> Toxicity tests commonly focus on cytotoxicity (damages cells), mutagenicity (alters genetic materials), carcinogenicity (causes cancer) and teratogenicity (causes birth defects).<sup>30</sup> The route of animal exposure may be determined by the most likely route of human exposure, bioavailability, practical difficulties and other considerations, so that more than one route of exposure to the test subject may be crucial.<sup>31</sup>

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<sup>25</sup> Ad hoc Interagency Coordinating Committee on the Validation of Alternative Methods Rep. On Validation and Regulatory Acceptance of Toxicological Test Methods, NIH Publication No. 97-3981 (March, 1997), at <http://iccvam.niehs.nih.gov/docs/guidelines/validate.pdf>.

<sup>26</sup> 40 C.F.R. § 799.9620(c) (2003).

<sup>27</sup> 40 C.F.R. § 799.9620(e) (*Id.* at (e)).

<sup>28</sup> 40 C.F.R. § 799.9620 (e)(7)(A) (2003).*Id.* at (7)(A).

<sup>29</sup> 40 C.F.R. § 799.9620 (e)(7)(B) (2003). *Id.* at (B).

<sup>30</sup> Joanne Zurlo, Deborah Rudacille, and Alan M. Goldberg, *supra* note 1.

<sup>31</sup> *Id.*

### A. *Animal Testing Practices*

Millions of animals are forced annually to ingest toxic substances and to have such rubbed into their eyes and lacerated skin. This is effected through two outmoded tests that have been repeated for decades and often used in duplicative studies.<sup>32</sup>

The LD/50 test is used to determine the acute toxicity of a substance.<sup>33</sup> This is the dose at which the test substance is lethal to 50% of the test animals.<sup>34</sup> During the test period the animal forcibly inhales, ingests or is otherwise exposed to the substance.<sup>35</sup> Often the animals involved experience acute distress including "pain, convulsions, discharge, diarrhea and bleeding from the eyes and mouth."<sup>36</sup>

The Draize test measures toxicity and corrosivity of chemicals applied to the eyes and abraded skin of rabbits.<sup>37</sup> The test is performed on the eyes of rabbits to test for corneal and conjunctival changes—i.e., irritation.<sup>38</sup> A substance is placed in the eye and the effects recorded at regular intervals.<sup>39</sup> This often causes irreparable damage to the eyes, including ulcers and bleeding, after which the animal is killed to investigate internal effects.<sup>40</sup> In the test for skin irritancy, the rabbit is first shaved and then its skin abraded by firmly pressing adhesive tape to its skin and ripping it off over a period of several days until several layers of skin have been exposed.<sup>41</sup> Thereafter the substance is applied to the raw flesh and effects recorded over a period of days or weeks of repeated applications.

### B. *Federal Animal Welfare Legislation*

In 1963, the National Institute of Health published the first set of guidelines on how to care for laboratory animals.<sup>42</sup> Three years later the Animal Welfare Act was passed by Congress and amended in 1985. It required that experiments be conducted so as to minimize animal pain and distress, through the use of anesthesia, medications and euthanasia.<sup>43</sup>

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<sup>32</sup> National Anti-Vivisection Society Homepage, at [http://www.navs.org/testing/animal\\_tests.cfm?SectionID=testing%20\(2001\)](http://www.navs.org/testing/animal_tests.cfm?SectionID=testing%20(2001)).

<sup>33</sup> Joanne Zurlo, Deborah Rudacille, and Alan M. Goldberg, *supra* note 1.

<sup>34</sup> *Id.*

<sup>35</sup> National Anti-Vivisection Society Homepage, *supra*, note 31.

<sup>36</sup> *Id.*

<sup>37</sup> *Id.*

<sup>38</sup> Joanne Zurlo, Deborah Rudacille, and Alan M. Goldberg, *supra* note 1.

<sup>39</sup> *Id.*

<sup>40</sup> National Anti-Vivisection Society Homepage, *supra* note 31.

<sup>41</sup> *Id.*

<sup>42</sup> Joanne Zurlo, Deborah Rudacille, and Alan M. Goldberg, *supra* note 1 at Appendix D.

<sup>43</sup> *Id.* aAt Appendix C.

However there is an exception when the researcher decides that the exclusion of any of the above is 'scientifically necessary'.<sup>44</sup>

### C. Shortcomings of Animal Tests

According to the Charter for the Scientific Advisory Committee on Alternative Toxicological Methods, alternative test methods "may provide improved prediction of adverse health effects compared to currently used methods or advantages in terms of reduced expense and time, reduced animal use, and reduced animal pain and distress. . ."<sup>45</sup>

#### 1. Costs

The expense of keeping and monitoring dozens of animals for weeks and months is much higher than that involved with several alternatives. Specialized tests, including immunotoxicity assays can cost over \$1,000,000 to assess one chemical via one route of exposure, in one species.<sup>46</sup> The cost-effectiveness of such bioassays is in dispute, as in order to complete a thorough test over a period of years, the expenditure of millions of dollars is required in order to test on only one species.<sup>47</sup> Acute toxicity tests cost about \$6,500 each for rats and repeated dose tests cost from \$40,000 for a 14-day exposure, to \$800,000 for a 2-year period of exposure.<sup>48</sup> In order to test thoroughly for toxic effects both acute and chronic in nature, tens of thousands of dollars per species tested must be spent.

#### 2. Suffering

Although many laboratory animals were bred and provided to experimenters for that purpose, this is not always the case. About 20% of all primates that are used are taken from their natural habitats in the wild, to be physically and psychologically harmed and then to die in captivity.<sup>49</sup> Half of the dogs and cats used in laboratories were former pets who were surrendered at animal control facilities and shelters, or given away and sold through newspaper advertisements.<sup>50</sup> These circumstances in addition to the captive breeding conditions of purpose-bred subjects amount to substantial deprivations and suffering before the physical harm of the toxicity testing is even inflicted upon the animals.

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<sup>44</sup> 7 U.S.C.A. § 2131(West 2003).

<sup>45</sup> Department of Health and Human Services, Charter for the Scientific Advisory Committee on Alternative Toxicological Methods (Dec. 18, 2001) at <http://iccvam.niehs.nih.gov/about/charter.pdf>. <http://iccvam.niehs.nih.gov/about/sacatm.htm>.

<sup>46</sup> American Council on Science and Health, *supra* note 19.

<sup>47</sup> *Id.*

<sup>48</sup> *Id.*

<sup>49</sup> Humane Society of the United States, *supra* note 6.

<sup>50</sup> *Id.*

### 3. Cross-species Differences

Practical problems associated with *in vivo* animal tests are cross-species biological differences that can lead to questionable test results. Differences among animals of the same species in addition to those differences with humans, have led to the premature approval of chemicals and products which later prove to be harmful and fatal to humans.

The U.S. General Accounting Office found that, of all new drugs marketed during a 10-year period, a majority — 52 percent, to be exact — had seriously toxic or even fatal effects that were not predicted by animal tests. And animal tests allow more minor side effects — rashes, nausea, diarrhea, etc. — to slip through routinely.<sup>51</sup>

A recent example is that of the prescription drug Baycol, which was recently withdrawn from the prescription drug market [Where or what was it withdrawn from?].<sup>52</sup> It was suspected to have caused at least 40 deaths due to a muscular side effect called rhabdomyolysis, wherein muscle cells are destroyed and enter into the blood stream causing pain, kidney failure and death.<sup>53</sup> Most of the animal experiments with similar drugs designed to reduce cholesterol (statins), yielded results opposite to those later experienced by humans and were subsequently recalled.<sup>54</sup>

Animal tests have also yielded inaccurate information as a result of flawed design protocol. For example, in 1977 saccharin was declared to be a human carcinogen by the FDA when test rats developed tumors as a result of their ingestion of the human equivalent of 1,000 cans of soda per day.<sup>55</sup> This result speaks nothing to the effects likely to be experienced by a human who consumes 1-6 cans per day. Likewise, the Multicenter Evaluation of In-Vitro Cytotoxicity (MEIC) program found that “while rat and mouse tests were only roughly 65 percent accurate in predicting human lethal blood concentrations of chemicals, a combination of human-cell tests predicted chemical toxicity with 80 percent precision.”<sup>56</sup>

## IV. THE MOVE TO ALTERNATIVES TO ANIMAL TESTING

For the foregoing reasons, headway has been made in the federal regulatory arena, and a new committee formed for the purpose of studying, developing and evaluating methods that will substantially replace, reduce or refine current tests that involve animals.

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<sup>51</sup> Neal Barnard, *Experiments on Animals Ineffective, Unnecessary*, Orlando Sentinel, April 7, 2002, at B1 (Op/Ed).

<sup>52</sup> National Anti-Vivisection Society Homepage, *supra* note 31.

<sup>53</sup> *Id.*

<sup>54</sup> *Id.*

<sup>55</sup> American Council on Science and Health, *supra* note 19.

<sup>56</sup> Neal Barnard, *supra* note 51.

A. *Interagency Coordinating Committee for the Validation of Alternative Methods*

The Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM or committee) was established in 1997 by the Director of the National Institute of Health (NIH), and made permanent pursuant to the ICCVAM Authorization Act of 2000.<sup>57</sup> The ICCVAM is an interagency coordinating committee of NIH under the National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM).<sup>58</sup> The purposes of the committee are to:

- (1) increase the efficiency and effectiveness of Federal agency test method review;
- (2) eliminate unnecessary duplicative efforts and share experiences between fed regulatory agencies;
- (3) optimize utilization of scientific expertise outside the federal government;
- (4) ensure that new and revised test methods are validated to meet the needs of federal agencies; and
- (5) reduce, refine, or replace the use of animals in testing, where feasible.<sup>59</sup>

The Act also established a permanent Scientific Advisory Committee for Alternative Toxicological Methods (SACATM) to provide guidance to the NICEATM and ICCVAM.<sup>60</sup> The ICCVAM is composed of the heads of fifteen federal regulatory and research agencies, including those of the Consumer Product Safety Commission, Food and Drug Administration, National Institutes of Health, Occupational Safety and Health Administration, and the Departments of Defense, Energy and the Interior.<sup>61</sup> The SACATM is itself composed of experts from the pharmaceutical, chemical and agricultural industries, as well as that of a national nonprofit animal protection organization.<sup>62</sup>

The mission that guides the NICEATM program and the ICCVAM is to develop, validate and gain regulatory acceptance of alternative test methods in accordance with the requirements of federal agencies.<sup>63</sup> In

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<sup>57</sup> ICCVAM Authorization Act of 2000, PL 106-545, §3(a), 114 Stat 2721. 2000. Interagency Coordinating Committee for the Validation of Alternative Methods, 42 U.S.C. § 2851-3(a) (West 2002). See also <http://iccvam.niehs.nih.gov/about/sacatm.htm>. (discussing the adoption of this law and the roles of the ICCVAM, NICEATM and SACATM).

<sup>58</sup> 42 U.S.C.A. § 201.

<sup>59</sup> *Id.* at (b).

<sup>60</sup> *Id.* at (d).

<sup>61</sup> *Id.* at (c). List is illustrative and non-exhaustive.

<sup>62</sup> *Id.* at (d)(2)(A)

<sup>63</sup> *Id.*

the ICCVAM Authorization Act of 2000, the term “alternative test method” is defined as a test method that

includes any new or revised test method; and (i) reduces the number of animals required; (ii) refines procedures to lessen or eliminate pain or distress to animals, or enhances animal well-being; or (iii) replaces animals with non-animal systems or one animal species with a phylogenetically lower animal species, such as replacing a mammal with an invertebrate.<sup>64</sup>

The committee carries out its functions by reviewing and evaluating proposed alternative test methods, facilitating interagency coordination of toxicological test protocols, providing guidance on the development of validation criteria, considering petitions from the public, and through its submission of test recommendations for alternative methods to appropriate federal agencies.<sup>65</sup> When the committee has been presented with sufficient information about a proposed test method, it will convene an expert peer review panel for the purposes of evaluating and validating the proposal.<sup>66</sup> Once the committee has approved a method it forwards the data and its recommendations to federal regulatory agencies for their review and possible adoption of the alternative method. The reviewing federal agency maintains discretion whether or not to adopt and incorporate the Committee’s recommended alternative test methods.<sup>67</sup>

Any federal agency that requires or recommends toxicological testing as part of a program must identify and forward to the committee any relevant test method that calls for an animal test for which the committee has validated an alternative. The agency must then adopt the committee’s recommendation unless the agency determines that the recommended test is inadequate in terms of biological relevance, hazard identification, dose-response assessment, or risk assessment; or that the recommendation will not adequately fulfill the needs of the agency in accord with its specific congressional mandate.<sup>68</sup>

#### 1. Regulatory acceptance

Prior to implementation of an alternative method by a government agency, it must be validated as a reliable and applicable replacement for the purpose specified. It must also be accepted, in that a regulatory or research agency has determined that it meets a specific regulatory need.<sup>69</sup>

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<sup>64</sup> ICCVAM Authorization Act of 2000, PL 106-545, §2, 114 Stat 2721. 2000.

<sup>65</sup> 42 U.S.C.A. § 201 (e).

<sup>66</sup> ICCVAM-NICEATM Overview, at: <http://iccvam.niehs.nih.gov/about/overview.htm>.

<sup>67</sup> ICCVAM Authorization Act of 2000, PL 106-545, §4, 114 Stat 2721. 2000.

<sup>68</sup> *Id.* at (e).

<sup>69</sup> Ad hoc Interagency Coordinating Committee on the Validation of Alternative Methods, *supra* note 25.

As agencies require testing for a variety of purposes and for different categories of substances, each agency will determine the suitability of the alternative method with regards to its purposes on a case-by-case basis.<sup>70</sup> ICCVAM procedural guidelines for approval of alternative methods state that the proposed method should include adequate data for chemicals used by the regulatory agency, hazard identification and dose-response assessment information, and the method should be able to be altered in accordance with similar testing needs of other agencies and international groups.<sup>71</sup> The method should also be time and cost effective and the subject of independent scientific peer review by parties who have no financial interest in the outcome of the evaluation.<sup>72</sup> The validation process should be flexible to comport with the increasing number and variety of scientific alternatives, but federal regulatory agencies should also force innovation.<sup>73</sup>

Agencies offer varying criteria for the acceptance or rejection of a test method for a specific purpose and there is no formal procedure for the interagency exchange of information in this regard.<sup>74</sup> Often an agency will even reject the testing guidelines of another agency pertaining to the same chemical substance.<sup>75</sup> ICCVAM summarizes the problem as follows:

Toxicology is a continually evolving science. New or revised tests. . . are constantly being developed. Established tests are reworked or improved, and new paradigms evolve. . . The evaluation of these procedures by individual agencies in isolation results in duplication of effort and may lead unnecessarily to inconsistent positions.<sup>76</sup>

For these reasons, ICCVAM is to serve as a forum for the exchange of information, the sharing of test data and the harmonization of test guidelines between government agencies and internationally, to "broaden the scientific and policy base, share limited resources, reduce review time and effort for any single authority, decrease testing demands on industry, reduce reliance on animal testing, and improve the risk assessment process."<sup>77</sup> Agencies are encouraged to review data and to participate in and contribute to the validation process from the initial proposal to its subsequent rejection, adoption or remand for further study.<sup>78</sup>

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<sup>70</sup> *Id.*

<sup>71</sup> *Id.*

<sup>72</sup> *Id.*

<sup>73</sup> *Id.*

<sup>74</sup> *Id.* at 3.2.1.

<sup>75</sup> *Id.* at 3.2.2.

<sup>76</sup> *Id.* at 3.7.

<sup>77</sup> *Id.* at 3.5.

<sup>78</sup> *Id.* at 3.7.

## 2. ICCVAM Test Method Validation

The process of validation entails that the test method be evaluated and found to be both reliable and relevant to a specific purpose.<sup>79</sup> Where a test has been designed to replace a currently employed method entirely, the standard for validation is that “use of the method will provide a comparable or better level of protection of human health or the environment than current methods or approaches.”<sup>80</sup> The results rendered by the new method will be compared with those yielded by the currently employed methods.<sup>81</sup> But where a new method is developed to identify new effects not previously tested or well defined, there is no paradigm with which to compare the effectiveness of the alternative.<sup>82</sup> In this regard, a substance may be validated for only a limited purpose, and validation status is revocable.<sup>83</sup> Generally, the process of validation will be simpler where the correlation between the measured effect and the predicted toxicological harm is the clearest.<sup>84</sup>

Note that a prerequisite to commencing the validation study is that all controls, methods, record-keeping procedures, protocols and preliminary subject data must be prepared and standardized in advance, so that the results are held to a rigid standard of accuracy.<sup>85</sup> The test results must also be reproducible within other qualified laboratories according to detailed procedural protocol.<sup>86</sup> This is accomplished in preliminary blind tests where the chemical codes are only revealed after the results have been obtained.<sup>87</sup>

### *B. Effect of ICCVAM Rules on California Law*

When a fed agency publishes acceptance of the method in the Fed register, it is officially adopted as an alternative to the traditional test for the purposes of the CA law.<sup>88</sup> Manufacturers and contract testing facilities are then banned from using the previously used animal testing method.<sup>89</sup> There is, however, an exception for medical research, in that this section does not apply, and such researchers are not restricted to the use of approved alternatives.<sup>90</sup>

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<sup>79</sup> *Id.* at 2.2.

<sup>80</sup> *Id.* at 2.3.

<sup>81</sup> *Id.* at 2.4.

<sup>82</sup> *Id.* at 2.3.

<sup>83</sup> *Id.* at 2.4.

<sup>84</sup> *Id.* at 2.4.

<sup>85</sup> *Id.* at 2.2.

<sup>86</sup> *Id.* at 2.4.2.1.

<sup>87</sup> *Id.* at 2.4.2.2.

<sup>88</sup> Cal. Civ. Code §1834.8 (a).

<sup>89</sup> *Id.*

<sup>90</sup> *Id.* at (e)(5). “Medical research” is defined as that “related to the causes, diagnoses, treatment, control, or prevention of physical or mental diseases and impair-

### C. *International Perspectives on Animal Experimentation*

One of the duties of the ICCVAM is to “facilitate appropriate inter-agency and international harmonization of acute or chronic toxicological test protocols that encourage the reduction, refinement, or replacement of animal test methods.”<sup>91</sup> ICCVAM recently coordinated its efforts with the Organization for Economic Cooperation and Development (OECD), an international regulatory commission comprised of 30 member-countries including Japan, Mexico, Canada and the U.S.<sup>92</sup> The OECD is instrumental in the acceptance of in vitro testing methods in the international regulatory community at large.<sup>93</sup> The OECD has accepted at least two alternatives to the acute oral toxicity LD/50 test, and after validation of the LLNA test by the ICCVAM, OECD also approved the method.<sup>94</sup> As a result of the peer review report on the LLNA method that was coordinated by ICCVAM and NICEATM prior to its validation, the OECD also accepted a new international test guideline (TG 429) for skin sensitization using LLNA.<sup>95</sup>

Likewise, the European Commission for the Validation of Alternative Methods (ECVAM) recently approved three new in vitro skin corrosivity tests and an in vitro phototoxicity assay.<sup>96</sup> In response NICEATM and ICCVAM developed an expedited review process for the evaluation of the methods, and the development of implementation guidelines for federal regulatory agencies.<sup>97</sup> Agency cooperation and reciprocity have facilitated the approval of alternative methods and serve to expedite the adoption of uniform guidelines.

## V. AVAILABLE ALTERNATIVE METHODS

### A. *Short Term Tests*

Federal agencies have yet to coordinate their efforts and construct a comprehensive interagency database of tested substances and results.<sup>98</sup>

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ments of humans and animals or related to the development of biomedical products, devices, or drugs. . . does not include the testing of an ingredient that was formerly used in a drug, tested for the drug use with traditional animal methods to characterize the ingredient and to substantiate its safety for human use, and is now proposed for use in a product other than a biomedical product, medical device, or drug.” *Id.* at (e)(5).

<sup>91</sup> 42 U.S.C. § 2851-3.

<sup>92</sup> Ad hoc Interagency Coordinating Committee on the Validation of Alternative Methods, *supra* note 25 at Appendix C.

<sup>93</sup> *Id.* at Appendix C.

<sup>94</sup> Interagency Coordinating Committee on the Validation of Alternative Methods, Annual Progress Report (Dec. 19, 2001).

<sup>95</sup> *Id.* at 7.

<sup>96</sup> ICCVAM-NICEATM The ICCVAM Homepage, *supra* note 66.

<sup>97</sup> *Id.*

<sup>98</sup> Different agencies keep their own inventories of substances.

As a practical matter, one obstacle is that each agency acts under a different directive, and generates different sets of guidelines for many of the same compounds.<sup>99</sup> As a result, many of the preliminary experiments involved in each project are duplicative of those having been performed previously by other agencies. To alleviate such inefficiencies testing program administrators have sought to reduce expensive duplication of initial tests on live animals via innovative methods.<sup>100</sup> Procedures known as short-term tests (STT) have risen in popularity as they can inexpensively identify lower-tier hazards within a matter of weeks.<sup>101</sup> STTs generally focus on chromosomal damage and genetic mutations to biological materials through in vitro assays.<sup>102</sup> These methods are less accurate than other long-term tests, but provide a strong preliminary screen indicative of mutagenic and carcinogenic effects.<sup>103</sup>

#### B. *In vitro* tests

In vitro tests incorporate methods for preserving organic materials, tissues and cells outside of the body.<sup>104</sup> Fragments of living tissue are extracted from the organism and propagated in vitro. The biological materials are exposed to substances and notations made of any latent effects.<sup>105</sup> Cell, tissue and organ cultures are used in highly controlled toxicity tests which are often less expensive than traditional tests.<sup>106</sup> These tests can predict the cellular and molecular effects of a substance on the specific tissue or organ, but do not provide the comprehensive response that the animal or human body would provide in vivo.<sup>107</sup> To bridge this gap, researchers have begun to co-culture cells from multiple organs, for the purposes of establishing how the substance might affect interrelated biological processes.<sup>108</sup> Tissue cultures provide a good screening mechanism and can reduce the number of animals used for preliminary tests.<sup>109</sup> They are also valuable for the approximation of human physiological response from animal data, for the purposes of assessing risk:

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<sup>99</sup> Timothy Riley, *Redressing the Silent Interim: Precautionary Action & Short Term Tests in Toxicological Risk Assessment*, 12 Risk: HEALTH SAFETY & ENV'T 281, 293 (2001).

<sup>100</sup> *Id.*

<sup>101</sup> *Id.*

<sup>102</sup> *Id.*

<sup>103</sup> *Id.* One study gave a predictive value for carcinogenic potential of 90% for bacterial bioassay STTs.

<sup>104</sup> Joanne Zurlo, Deborah Rudacille, and Alan M. Goldberg, *supra* note 1.

<sup>105</sup> *Id.*

<sup>106</sup> *Id.*

<sup>107</sup> *Id.*

<sup>108</sup> *Id.*

<sup>109</sup> *Id.*

For extrapolation to effects on intact humans, the most effective approach may be to compare effects on a small number of living animals with effects on cultured cells from the same species, and then to compare species differences in cell culture responses. Such comparisons should be both the basis for making cell culture to whole animal correlations and an insight into species-specific differences in response to the test substances, both of which facilitate extrapolation to potential effects on intact humans.<sup>110</sup>

In vitro tissue tests are also bolstered by computer models that can predict physiological and metabolic effects on the whole body through the use of equations gleaned largely from prior live animal experiments.<sup>111</sup>

Tissue slices are also used for a number of explants including kidney and liver. These segments retain the differentiated functions that the organ would have if it were intact in the live animal.<sup>112</sup> The slice maintains its cellular heterogeneity and three-dimensional integrity in vitro, so that it is paradigmatic for comparisons with in vivo tests.<sup>113</sup> The use of tissue slices can also reduce the number of test animals needed, as over one hundred slices can be prepared from the liver of one rodent.<sup>114</sup> Slices can also be used to study the normal functions of diseased tissues and tumors.<sup>115</sup>

Another benefit of in vitro cell cultures is the ability to test human tissue. At present, most research is conducted on nonhuman animals, although the majority of this data is collected for the purpose of predicting human response.<sup>116</sup> Differences among species pertaining to cellular regulatory and metabolic processes mean that the effect on a nonhuman culture will not necessarily correspond to that on human cells.<sup>117</sup> For example, in a comparison of human, rat and rabbit nasal turbinate cells in response to tetradecanoylphorbol-13-acetate, the compound was found to be severely toxic to human cells, had a minor stimulant effect on cell replication in the rat cells, but caused no detectable effect on the rabbit cells.<sup>118</sup>

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<sup>110</sup> Johns Hopkins University, Center for Alternatives to Animal Testing, Cell Culture Systems and In Vitro Toxicity Testing, a report of the technical workshop of June 13-15 1990, at [http://caat.jhsph.edu/pubs/tech\\_reports/techreport04.htm](http://caat.jhsph.edu/pubs/tech_reports/techreport04.htm).

<sup>111</sup> Joanne Zurlo, Deborah Rudacille, and Alan M. Goldberg, *supra* note 1.

<sup>112</sup> Center for Alternatives to Animal Testing, *supra* note 110.

<sup>113</sup> *Id.*

<sup>114</sup> *Id.*

<sup>115</sup> *Id.*

<sup>116</sup> *Id.* at 21.

<sup>117</sup> *Id.*

<sup>118</sup> *Id.*

## 1. Murine Local Lymph Node Assay (LLNA)

The Murine Local Lymph Node Assay (LLNA) is a test used to determine allergic dermatitis as a result of exposure of chemicals to the skin.<sup>119</sup> It replaces currently accepted guinea pig tests, uses fewer animals (1/3-1/2 the amount subjected previously), and virtually eliminates pain and distress.<sup>120</sup> Mice are used instead of guinea pigs, and a chemical that affects lymph nodes applied to their ears.<sup>121</sup> As a result toxicity is perceived in an earlier and less painful stage.<sup>122</sup> LLNA yields results after a shorter test duration and unlike the traditional test, also yields dose-response information.<sup>123</sup> This method was approved by ICCVAM in 1999, and its validation published in the final peer review report of the panel in February of that year.<sup>124</sup> Following shortly thereafter, the EPA, FDA, and OSHA each announced its acceptance of the method.<sup>125</sup> An implementation workshop was convened in 2001, co-sponsored by ICCVAM and the International Life Sciences Institute, to discuss methods of conducting the test and interpreting results in accord with regulatory agency requirements.<sup>126</sup>

## 2. Corrositex®

Corrositex is another alternative method that has been reviewed and accepted for implementation by the ICCVAM.<sup>127</sup> It is an *in vitro* method used to determine the corrosivity of largely acidic chemicals on the skin. Corrositex refines and reduces animal use, and partially replaces the traditional rabbit skin test.<sup>128</sup> It will completely replace the use of live animals in some cases, while in others reducing the number of animals used from three per chemical tested to only one.<sup>129</sup> This reduction becomes numerically significant in the context of tests performed annually, as there are more than two thousand chemicals introduced and submitted for approval each year.<sup>130</sup>

The test works by introducing the potential toxin *in vitro* to a collagen matrix barrier that functions as an artificial skin.<sup>131</sup> The test is timed

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<sup>119</sup> ICCVM-NICEATM The ICCVAM homepage, *supra* note 66.

<sup>120</sup> *Id.*

<sup>121</sup> *Id.*

<sup>122</sup> *Id.*

<sup>123</sup> *Id.*

<sup>124</sup> *Id.*

<sup>125</sup> *Id.*

<sup>126</sup> *Id.*

<sup>127</sup> *Id.*

<sup>128</sup> *Id.*

<sup>129</sup> NIEHS Press Release #10-99 (June 22, 1999), at <http://www.niehs.nih.gov/oc/news/corros.htm>.

<sup>130</sup> *Id.*

<sup>131</sup> *Id.*

from the moment of introduction of the chemical, until it has penetrated the barrier and caused a color change in pH indicator dyes.<sup>132</sup> The reaction time is then compared to a classification chart to determine corrosivity.<sup>133</sup> The ICCVAM has approved Corrositex for the replacement of the *in vivo* test under certain circumstances, and as part of a tiered testing strategy, for preliminary toxicity screening.<sup>134</sup>

### 3. EpiDerm™ and EPISKIN™

EpiDerm™ and EPISKIN™ are species-specific methods for assessing the corrosivity of a chemical to the human skin.<sup>135</sup> These are three-dimensional *in vitro* tissue cultures of human skin to which the test chemical is applied and cell death recorded throughout a defined exposure period.<sup>136</sup> These methods are currently under an expedited review process by the ICCVAM, as the European Center for the Validation of Alternative Methods (ECVAM) recently completed its process of validation and forwarded data to the committee for its review.<sup>137</sup> This interagency accelerated approval process aids in the avoidance of test duplication and unnecessary expenditure of governmental resources and time.<sup>138</sup> The ability to conduct tests on human tissues without any risk to individuals will usher forth toxicity testing into a new era.

#### C. Human Tissue

In recent years the availability of human tissues has greatly increased so that several organizations now provide cultures and cell lines, as well as toxicity testing services.<sup>139</sup> A report of the Center for Alternatives to Animal Testing at Johns Hopkins University, predicts that the majority of preliminary cell line toxicity tests will be performed by contract laboratories, which will then be able to specialize and refine their methods.<sup>140</sup> The main obstacle to more wide spread human tissue culturing is the ensuing ethical and legal considerations.

Policy issues regarding ownership and profit distribution are some of the ethical dilemmas that have surfaced in the context of human tissue extraction.<sup>141</sup> Donors may or may not receive compensation, depending upon the organization with which they donate, and their samples will

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<sup>132</sup> *Id.*

<sup>133</sup> *Id.*

<sup>134</sup> *Id.*

<sup>135</sup> Interagency Coordinating Committee on the Validation of Alternative Methods, Annual Progress Report (Dec. 19, 2001) at 9, *supra* note 95.

<sup>136</sup> *Id.*

<sup>137</sup> *Id.*

<sup>138</sup> *Id.*

<sup>139</sup> *Id.* at 22.

<sup>140</sup> Center for Alternatives to Animal Testing, *supra* note 110.

<sup>141</sup> *Id.* at 25.

each have different scientific and monetary values depending upon the health of the donor and the substance to be tested.<sup>142</sup> Although samples may be stored anonymously, prior to collection extensive pathological information will have to be solicited from the subject in order to maintain accurate data and controls on the experiments.<sup>143</sup> As a result, the scientific value of a sample can often be determined before it is collected and stored as anonymous material.

The problems inherent to this process have surfaced through legal disputes over ownership of extracted and stored cells. For example, in *Moore v. Regents of the University of California*, the court held that the plaintiff had no expectation of retaining ownership of cells excised from his body, and therefore no interest in the cell line that was propagated and patented.<sup>144</sup> However, in *Hecht v. Superior Court*, a case over the disposition of the stored sperm of a decedent, the court determined that because the decedent had an expectation that he would retain control over the materials, and so the sperm was viewed as property and subject to ownership and transfer in accordance with the probate codes.<sup>145</sup> In this sense, expectation can play an important part in determining such claims to ownership or control. It should be noted that human sperm is unique in that it represents potential human life to the owners, whereas other human tissues have value that is measured by utility to the recipient or value of information to be gleaned from the experiment. The issue of control should play a smaller part in disputes over other (non-reproductive) extracted tissues once the donor has been compensated.

Another option is to reject the idea of compensating donors for their tissues. Women and men are compensated for donating genetic materials to banking services that sell them to buyer-patients who wish to create a human life. In the case of organ donation though, facilities are required to be non-profit and to operate in an equitable manner, which precludes the prioritization of financial gain.<sup>146</sup> As an alternative to private ownership, it has been suggested that blood banking practices serve as the paradigm, wherein people are encouraged to donate as a matter of good will.<sup>147</sup> In the context of blood, this idea has been largely successful and many repeat donors do so on a regular basis. It seems that people are anxious to give of themselves when they perceive a direct benefit to an individual in need. Marrow, blood and organ donors receive gratification from the expectation that they may save individual lives. Attitudes may

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<sup>142</sup> *Id* at 26.

<sup>143</sup> *Id* at 25.

<sup>144</sup> *Moore v. Regents of the Univ. of Cal.*, 793 P.2d 479 (Cal. 1990).

<sup>145</sup> *Hecht v. Superior Court*, 20 Cal. Rptr. 2d 275 (Ct. App. 1993).

<sup>146</sup> 42 U.S.C.A. § 273. (West 2002).

<sup>147</sup> Sheila R. Kirschenbaum, *Banking on Discord: Property Conflicts in the Transplantation of Umbilical Cord Stem Cells*, 39 ARIZ. L. REV. 1391 (1997).

be different though in the context of collection of purely experimental materials, where the good to be produced is far more remote. If this is the case, financial inducement may prove to be necessary, wherein a standard fee system would probably best serve public policy. Human tissue extrapolation is comparable to blood or marrow donation and should entail minimal "costs" or health detriments to the donor, to be distinguished from the unconscionable sale of human body parts generally.

#### D. Cell Lines

Once a successful primary culture has been made of cells, tissues or organs taken from the organism, the materials can be subcultured and developed into a cell line.<sup>148</sup> The lifespan of the line may be finite or infinite, and various functions can be altered.<sup>149</sup> As early as 1911, toxicity tests were conducted on a cell line that had been propagated for 34 years and originated in the heart of a chick embryo.<sup>150</sup>

Stem cells in particular are often more sensitive to toxins than are other cells.<sup>151</sup> Stem cells are capable through successive duplications of differentiating into mature cells of a specific tissue type.<sup>152</sup> In 1998 it was discovered that stem cells taken from a human embryo can be cultured under conditions that cause them to differentiate into any other type of cell.<sup>153</sup> Stem cell lines replicate indefinitely and in the process create new lines in addition to differentiated cells.<sup>154</sup> In the future, this capability could be utilized to transplant healthy cells into the affected site and replace damaged or diseased human tissue, creating a variety of alternative therapies.<sup>155</sup>

In recent research on mice, for example, it was found that embryonic stem cells injected into the heart of the adult mouse were incorporated perfectly into the heart muscle of the adult animal, that is, they differentiated into heart muscle cells and became perfectly synchronized with the beat of the host heart.<sup>156</sup>

The problem with human stem cell collection, is that at present the most versatile type of these cells originates in a human fetus, the development of which is arrested at the blastocyte stage (day 5 or 6 after con-

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<sup>148</sup> Center for Alternatives to Animal Testing, *supra* note 110.

<sup>149</sup> *Id.*

<sup>150</sup> Joanne Zurlo, Deborah Rudacille, and Alan M. Goldberg, *supra* note 1.

<sup>151</sup> Center for Alternatives to Animal Testing, *supra* note 110.

<sup>152</sup> Governo Italiano, Opinion of the National Bioethics Committee on the Therapeutic Use of Stem Cells (Oct. 27, 2000) at <http://www.palazzochigi.it/bioetica/english/cells.html>.

<sup>153</sup> *Id.*

<sup>154</sup> *Id.*

<sup>155</sup> *Id.*

<sup>156</sup> *Id.*

ception), and the stem cells isolated and extracted.<sup>157</sup> This process entails that a human fetus be sacrificed at the right time in its development so that the cells may be procured. The ethical implications involved are complex, as currently the common method for the collection of such tissue is in the process of voluntary or spontaneous fetal abortion procedures.<sup>158</sup> Stem cells have been extracted from other sources including adult tissues (blood, bone marrow, endothelium, nervous system, and muscle), blood from the umbilical cord and embryos.<sup>159</sup> Of the types extractable from adult tissues, bone marrow cells are the most sustainable in the undifferentiated state—that analogous to tissues derived from human fetal tissues.<sup>160</sup> Cells extracted from the other adult human tissues are more difficult to isolate and to maintain in an undifferentiated state.<sup>161</sup>

In the future, nuclear transplant techniques (i.e., “cloning”) may solve this problem.<sup>162</sup> As tested on certain animals (recall the sheep “Dolly”), the technique has so far been able to render embryos without the use of sperm.<sup>163</sup> In the case of humans, where stem cells are extracted from a blastocyte (5-6 day embryo),

the stem cells derived from the blastocytes not only behave like stem cells derived from an embryo generated by the union of sperm and egg, but could also afford the substantial advantage of being genetically identical to the cells of the person from which the nucleus was extracted, thus avoiding all problems of rejection of the cell transplant in the case in which the nucleus donor is a patient and the cell transplant is aimed at repairing damage to diseased tissue in him (auto-transplant).<sup>164</sup>

Cloning would entail the propagation of infinite cell lines at the expense of one human fetal blastocyte, and in terms of utility would offer multitude distributive benefits to successive generations. This sacrifice should pose less of an ethical dilemma in jurisdictions where abortion is legal. Once it is known that a fetus will be disposed of, one can argue that it would be sounder policy to utilize rather than waste such a resource. Here an analogy to *Moore* (infra) can be made: the patient has no expectation to retain control over the materials and so no property interest inheres.

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<sup>157</sup> *Id.*

<sup>158</sup> *Id.*

<sup>159</sup> *Id.*

<sup>160</sup> *Id.*

<sup>161</sup> *Id.*

<sup>162</sup> *Id.*

<sup>163</sup> *Id.*

<sup>164</sup> *Id.*

## VI. CONCLUSION

According to the Humane Society of the United States, animal experimentation has greatly declined in the last twenty years, and in vitro testing rapidly increased.<sup>165</sup> Several consumer product companies have been supportive of alternative testing methods: over twenty years ago Revlon funded research at Rockefeller University toward the development of alternative test methods, and the Noxell and Avon Cosmetics Corporations both implemented alternatives to the draize eye test in 1989.<sup>166</sup> It would seem that legislators, the public and some governmental and private industries are anxious to alleviate animal suffering and to find innovative methods for toxicity testing.

Interagency coordination is pivotal in the area of domestic and international regulatory acceptance of alternative test methods. Information sharing reduces costs of testing and can refine methods so as to reduce the number of test animals subjected. Steps have been taken to substantially advance this goal, and it appears through the formation of various committees that many of the economic world-leaders would prefer to revise animal testing methods both for the advancement of human health and the reduction of animal suffering. Economic considerations also weigh in favor of interagency coordination, as duplicative studies are wasteful of time and resources as well as animal bodies.

Finally, innovative new methods are able to provide human materials with no physical harm to human individuals. The results of toxicity tests relying upon these materials provide uniquely accurate results specifically geared towards human effects. Generally this process entails financial benefits as well, but such may not always be the case. The value of human-specific results is so great that it should be the primary factor for consideration in regulatory acceptance. Guidelines pertaining to the extraction of human materials would be helpful in the determination of ownership and control issues which arise in this context. Altruistic individuals may choose to donate short of such regulations for the benefit of human kind, and these individuals should be allowed to do so if that is their wish.

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<sup>165</sup> Humane Society of the United States, *supra* note 6.

<sup>166</sup> *Id.*

